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(71) Demandeur/Applicant:
REGENERON PHARMACEUTICALS, INC., US
(72) Inventeurs/Inventors:
LIGOCKI, ANN J., US;
ROMANO, CARMELO, US
(74) Agent: MCCARTHY TETRAULT LLP

(54) Titre : VECTEURS VIRUS ADENO-ASSOCIE ET PROCEDES D'ADMINISTRATION D'AGENTS THERAPEUTIQUES
(54) Title: ADENO-ASSOCIATED VIRUS VECTORS FOR THE DELIVERY OF THERAPEUTICS

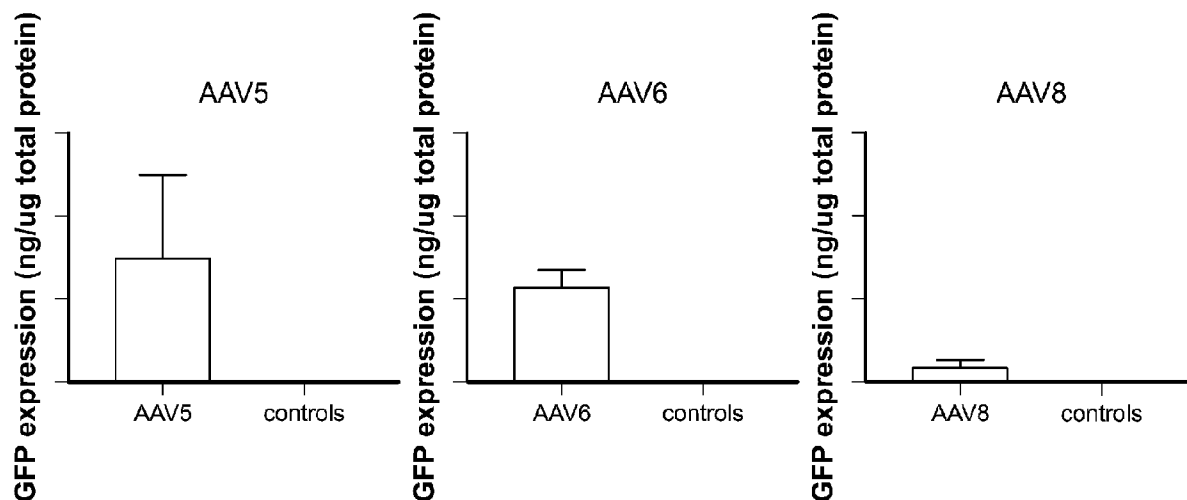


FIG. 9

(57) **Abrégé/Abstract:**

Provided herein are methods for selectively delivering therapeutics to the eye using AAV vectors. For example, the cornea can be specifically targeted using the methods described. Also provided herein are compositions comprising AAV vectors packaged with CRISPR complexes, which can be delivered directly to the eye, for example the cornea, and in particular the cornea endothelium. Diseases and conditions comprising abnormalities or deterioration of tissues in the eye, such as the cornea endothelium (e.g. FECD), can be treated using the methods and compositions described herein.

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(71) Applicant: **REGENERON PHARMACEUTICALS, INC.**, [US/US]; 777 Old Saw Mill River Road, Tarrytown, NY 10591-6707 (US).

(72) Inventors: **LIGOCKI, Ann J.**; c/o Regeneron Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591-6707 (US). **ROMANO, Carmelo**; c/o Regeneron

Pharmaceuticals, Inc., 777 Old Saw Mill River Road, Tarrytown, NY 10591-6707 (US).

(74) Agent: **ACHKAR, Charles C.** et al.; Ostrolenk Faber LLP, 845 Third Avenue, 8th Floor, New York, NY 10022 (US).

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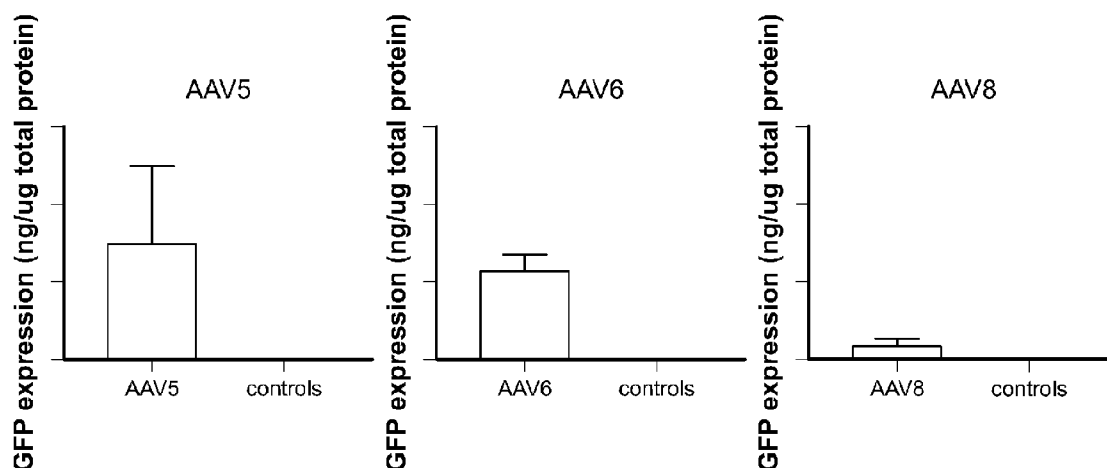


FIG. 9

(57) Abstract: Provided herein are methods for selectively delivering therapeutics to the eye using AAV vectors. For example, the cornea can be specifically targeted using the methods described. Also provided herein are compositions comprising AAV vectors packaged with CRISPR complexes, which can be delivered directly to the eye, for example the cornea, and in particular the cornea endothelium. Diseases and conditions comprising abnormalities or deterioration of tissues in the eye, such as the cornea endothelium (e.g. FECD), can be treated using the methods and compositions described herein.

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ADENO-ASSOCIATED VIRUS VECTORS FOR THE DELIVERY OF THERAPEUTICS**CROSS REFERENCE TO RELATED APPLICATIONS**

[001] This application claims priority to U.S. Provisional Application Nos. 62/812,017 filed February 28, 2019; 62/831,838 filed April 10, 2019; and 62/878,865 filed July 26, 2019, each of which is hereby incorporated in its entirety.

SEQUENCE LISTING

[001.1] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on June 3, 2020, is named 67000-1023_WO_SL.txt and is 357,652 bytes in size.

FIELD OF THE INVENTION

[002] The present invention is generally directed to using adeno-associated virus (AAV) vectors to deliver therapeutics to the eye, for example to the corneal endothelium. The present invention is also directed to compositions comprising the AAV vectors. Corneal dystrophies can be treated with the methods and compositions of the present invention.

BACKGROUND

Adeno-associated virus (AAV) is a small, replication-deficient parvovirus. AAV is about 20-24 nm long, with a density of about 1.40-1.41 g/cc. AAV contains a single-stranded linear genomic DNA molecule approximately 4.7 kb in length. The single-stranded AAV genomic DNA can be either a plus strand, or a minus strand. AAV contains two open reading frames, Rep and Cap, flanked by two 145 base inverted terminal repeats (ITRs). AAVs contain a single intron. Cis-acting sequences directing viral DNA replication (Rep), encapsidation/packaging and host cell chromosome integration are contained within the ITRs. Three AAV promoters, p5, p19, and p40 (named for their relative map locations) drive the expression of the two AAV internal open reading frames encoding rep and cap genes. The p5 and p19 are the rep promoters. When coupled with the differential splicing of the single AAV intron, the two rep promoters result in the production of four rep proteins (rep 78, rep 68, rep 52, and rep 40) from the rep gene. The rep proteins have multiple enzymatic properties that are responsible for replicating the viral genome. The cap gene is expressed from the p40 promoter, and encodes the three capsid proteins VP1, VP2, and VP3. Alternative splicing and non-consensus translational start sites are responsible for the production of the three related capsid proteins. A single polyadenylation site is located at map position 95 of the AAV genome. Muzyczka reviews the life cycle and genetics of AAV (Muzyczka, *Current Topics in Microbiology and Immunology*, 158:97-129 (1992)).

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[004] AAV infection is non-cytopathic in cultured cells. Natural infection of humans and other animals is silent and asymptomatic (does not cause disease). Because AAV infects many mammalian cells, there is the possibility of targeting many different tissues *in vivo*. In addition to dividing cells, AAV transduces slowly dividing and non-dividing cells, and can persist essentially for the lifetime of those cells as a transcriptionally active nuclear episome (i.e. extrachromosomal element). The AAV proviral genome is infective as cloned DNA in plasmids, which makes construction of recombinant genomes possible. Moreover, because the signals directing AAV replication, genome encapsidation, and integration are all contained within the ITRs of the AAV genome, some or all of the approximately 4.3 kb of the genome, encoding replication and structural capsid proteins (rep-cap) are contained within the ITRs of the AAV genome, and can be replaced with heterologous DNA, such as a gene cassette containing a promoter, a DNA of interest, and a polyadenylation signal. The rep and cap proteins may be provided in trans. AAV is a very stable and robust virus, and easily withstands conditions used to inactivate adenovirus (56°C to 65°C for several hours), therefore cold preservation of AAV is less critical. And, AAV-infected cells are not resistant to super-infection. These unique properties of AAV make it useful as a vector for delivering foreign DNA to cells or subjects, for example, in gene therapy.

[005] Corneal dystrophy is a term for the heterogeneous group of non-inflammatory bilateral diseases restricted to the cornea. They are grouped by the anatomical location within the cornea of the pathology. Most do not have any manifestations outside of the cornea and they result with corneal opacities and affect visual acuity (see <https://www.cornealdystrophyfoundation.org/what-is-corneal-dystrophy>).

[006] The cornea has three major regions that are affected by corneal dystrophies: corneal epithelium, stroma, endothelium. Anterior corneal dystrophies affect the corneal epithelium and its basement membrane and the superficial corneal stroma. Stromal corneal dystrophies affect the corneal stroma. Posterior corneal dystrophies affect Descemet membrane and the corneal endothelium. The most common posterior corneal dystrophy is Fuchs' corneal endothelial dystrophy.

[007] Recently, it has been found that certain pathological conditions or diseases are associated with mutations in the *TCF4* gene, coding for transcription factor 4 protein (TCF4). Diseases associated with mutations in the *TCF4* gene include Fuchs endothelial corneal dystrophy (FECD), posterior polymorphous corneal dystrophy (PPCD), primary sclerosing cholangitis (PSC), Pitt-Hopkins syndrome, distal 18q deletion, and schizophrenia.

[008] FECD is a condition that causes vision problems. It affects the cornea of the eye, in particular the endothelium. The cornea is located on the front surface of the eye, and corneal tissue contains five basic layers. The epithelium is the cornea's outermost layer. The epithelium functions to block the passage of foreign material (e.g. dust, water, bacteria) into the eye and other layers of the cornea, and provides a smooth surface to absorb oxygen and cell nutrients from tears, distributing these nutrients to the rest of the cornea. The epithelial cells anchor and organize themselves on the basement membrane of the epithelium. Lying directly below the basement membrane of the epithelium is the Bowman's layer, which is a transparent sheet of tissue composed of collagen fibers. Beneath Bowman's layer is the stroma. The stroma comprises about 90% of the cornea's thickness, and consists primarily of water and collagen. A thin, strong sheet of tissue, Descemet's membrane is beneath the stroma. Descemet's membrane is composed of collagen fibers, and is made by the endothelial cells that lie beneath it. The endothelium is the layer below Descemet's layer.

[009] The endothelium is the extremely thin innermost layer of the cornea and is vital to keeping the cornea clear. The corneal endothelium is a monolayer of amitotic cells that form a barrier between the corneal stroma and the aqueous humor. The corneal endothelial cells function by pumping fluid from the cornea to maintain the cornea at the correct thickness to preserve clarity. In some posterior corneal dystrophies, such as FECD, the corneal endothelium is diseased and cells die over the course of this progressive disease. As these cells die, the remaining cells expand to fill the space, and the layer loses the ability to properly function. This results in corneal edema and increased opacity, leading to a reduction in visual acuity. In advanced stages of the disease, blindness may ensue. Loss of vision due to FECD is the leading cause of corneal transplants in the USA.

[0010] Because the corneal endothelium is affected in these diseases, targeting them to deliver therapeutics could aid in stopping the progression of disease. One such methodology is adeno-associated viruses (AAVs), which can be packaged to deliver the therapeutic, and

delivered via intracameral or intrastromal injection to come into contact with the cornea endothelium. Proteins or nucleotide sequences are commonly packaged into AAV vectors.

[0011] It has been suggested that genetic factors are associated with the occurrence of FECD. Genetic loci known to be associated with FECD include *FCD1* to *FCD4*, *ZEB1/TCF8*, *SLC4A11*, *LOXHD1*, and *COL8A2*. One such genetic factor is trinucleotide repeat (TNR) expansions in the *transcription factor 4 (TCF4)* gene. Most of the genetic predisposition for FECD is associated with a TNR in the third intron of the *TCF4* gene. A repeat length of greater than 50 repeats is generally associated with a clinical diagnosis of FECD (Wieben et al., *PLOS One*, 7:11, e49083 (2012)). Recently, it has been suggested that this TNR expansion causes aggregation of the affected *TCF4* RNA, and sequestration of key RNA splicing factors (Mootha, et al., *Invest. Ophthalmol. Vis. Sci.*, 55(1):33-42 (2014); Mootha, et al., *Invest. Ophthalmol. Vis. Sci.*, 56(3):2003-11 (2015); Vasanth, et al., *Invest. Ophthalmol. Vis. Sci.*, 56(8):4531-6 (2015); Soliman et al., *JAMA Ophthalmol.*, 133(12):1386-91 (2015)). Sequestration of RNA splicing factors can lead to global changes in gene expression, resulting in significant changes in cellular function, and cell death (Du et al., *J. Biol. Chem.*, 290:10, 5979-5990 (2015)).

[0012] Another genetic mutation that is associated with FECD occurs in the *COL8A2* gene (Vedana et al., *Clinical Ophthalmology*, 10, 321-330 (2016)). Collagen VIII, or COL8 (comprising COL8A1 and COL8A2) is regularly distributed in the Descemet's membrane of the cornea. It has been shown that corneas from patients with mutations in *COL8A2* have an irregular mosaic deposition of different amounts of COL8A1 and COL8A2, in a non-coordinated manner. Three point mutations of the *COL8A2* lead to intracellular accumulation of mutant COL8 peptides. These point mutations are Gln455Lys, Gln455Val, and Leu450Trp. The intracellular accumulation of mutant COL8 peptides can cause early-onset FECD, as well as the related corneal disorder PPCD (which is characterized by changes in the Descemet's membrane and endothelial layer of the cornea).

[0013] Although AAV vectors have been used to deliver gene editing therapeutics directly to the eye, this has generally only been shown for posterior portions of eye, such as the retina. Delivery of gene editing therapeutics to the anterior portions of the eye, such as the cornea, is far less well researched and documented. There remains a need to develop delivery

techniques that can preferentially deliver therapeutics only to specific areas of the eye and to specific tissues or cells, particularly the anterior portions such as the cornea.

SUMMARY OF THE INVENTION

[0014] The present invention provides a method of delivering a therapeutic to the corneal endothelium, to treat diseases such as corneal dystrophies, for example, FECD. The methods of the invention utilize AAVs to deliver therapeutics directly to the eye, particularly the corneal endothelium. In certain embodiments, the AAVs are packaged with proteins, or nucleotides encoding the proteins, to be expressed in certain cells of the eyes. In other embodiments, the AAVs are packed with a CRISPR RNP complex (i.e. a complex with a Cas protein) to elicit directed gene editing in the eye, and in specific areas or cells of the eye. In some embodiments, the AAVs are packaged with a CRISPR gRNA complexed with a nucleotide sequence encoding a Cas protein. The present invention also provides compositions comprising the AAVs.

[0015] In a particular aspect, the present invention provides a composition comprising:

- a) a nucleotide sequence, or portion thereof, of an AAV vector; and
- b) a nucleic acid editing system comprising at least one nucleotide sequence that is complementary to at least one mutant allele on a target gene associated with diseases or conditions in the cornea; a nucleic acid capable of down-regulating gene expression of at least one mutant allele on a target gene associated with diseases or conditions in the cornea; and/or at least one nucleotide sequence, or portion thereof, that codes for a protein to be expressed in the eye.

[0016] In a another aspect, the present invention provides a method of expressing a protein in an eye of a subject in need thereof comprising:

- a) providing one or more adeno-associated (AAV) vectors comprising a nucleotide sequence that encodes said protein; and
- b) administering the AAV vector to the eye.

[0017] In another aspect, the present invention provides a method for repairing a gene expressed in the cornea in a subject in need thereof, the method comprising:

a) providing a delivery system comprising a nucleic acid editing system comprising at least one nucleotide sequence that is complementary to at least one mutant allele on a target gene associated with diseases or conditions in the cornea; and

b) administering the delivery system to the cornea of the subject.

When the term “repairing” is used, it is also meant to include inducing repair.

[0018] In yet another aspect, the present invention provides a method of treating a disease or condition of the cornea caused by a mutant allele of a gene that comprises trinucleotide repeats (TNRs) and/or a point mutation in a subject in need thereof, said method comprising:

- a) excising at least a portion of the trinucleotide repeats (TNRs) within the gene, comprising:
 - i) providing an AAV5, AAV6, or AAV8 vector which comprises one or more nucleotide sequences coding for one or more guide RNAs targeting a sequence within the TNRs, 5' of the TNRs, 3' of the TNRs, or combination thereof; and
 - ii) administering the vector to the cornea; and/or
- b) correcting the point mutation of the gene or gene product comprising:
 - i) providing an AAV5, AAV6, or AAV8 vector comprising one or more nucleotide sequences coding one or more guide RNAs targeting a sequence in the gene associated with a point mutation in the gene product; and
 - ii) administering the vector to the cornea;

wherein said one or more nucleotide sequences are preferentially expressed in the cornea after intracameral injection.

[0019] In another aspect, the present invention provides a method of treating a disease or condition of the cornea caused by a mutant allele of a gene that comprises trinucleotide repeats (TNRs) and/or a point mutation in a subject in need thereof, said method comprising:

- a) excising at least a portion of the trinucleotide repeats (TNRs) within the gene, comprising:
 - i) providing an AAV5, AAV6, or AAV8 vector which comprises one or more nucleotide sequences coding for one or more guide RNAs targeting a sequence within the TNRs, 5' of the TNRs, 3' of the TNRs, or combination thereof; and
 - ii) administering the vector to the cornea; and/or

- b) Correcting the point mutation of the gene or gene product comprising:
 - i) providing an AAV5, AAV6, or AAV8 vector comprising one or more nucleotide sequences coding one or more guide RNAs targeting a sequence in the gene associated with a point mutation in the gene product; and
 - ii) administering the vector to the cornea.

[0020] In another aspect, the present invention provides a method for down-regulating expression of a cornea gene in a subject in need thereof, the method comprising administering to the subject a delivery system comprising:

- a) a nucleotide sequence, or portion thereof, of an AAV vector;
- b) a nucleic acid capable of down-regulating gene expression of at least one mutant allele on a target gene associated with diseases or conditions in the cornea; and
- c) administering the delivery system to the cornea.

[0021] In another aspect, the present invention provides a method of preferentially expressing a protein in endothelial cells of the cornea in a subject in need thereof, comprising:

- a) providing one or more adeno-associated (AAV) vectors comprising a nucleotide sequence, or portion thereof, that encodes said protein; and
- b) administering the AAV vector to the cornea.

[0022] These and other objects, advantages, and features of the invention will become apparent to those persons skilled in the art upon reading the details of the compositions and methods as more fully described below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] **Figure 1:** Figure 1 is an illustration of the layers of the cornea (see <https://discoveryeye.org/treatment-corneal-scratches-and-abrasions/>).

[0024] **Figure 2:** Figure 2 is an illustration of the structure of the mouse eye, and a depiction of intracameral and intravitreal injection into the eye.

[0025] Figure 3: Figure 3 depicts the in vivo images of a mouse eye after intracameral delivery of AAV5-eGFP. Panels A-D show images from the OD eye (“OD” refers to Oculus Dexter which is latin for the right eye). Panels E-H show images from the OS eye (“OS” refers to Oculus Sinister which is latin for the left eye). Panel A provides a reference for panel B. Panel E provides a reference for panel F. Panels B & F show the image which demonstrates fluorescence in the cornea from the AAV5-eGFP. Panels C & G shows the fundus image and panels D & H show the image which demonstrates no fluorescence in the retina. Two dots of fluorescence are detected in the OS retina shown by arrows in panel H.

[0026] Figure 4: Figure 4 depicts the immunohistochemistry of the same eyes shown in Fig. 3. AAV5-eGFP was delivered by intracameral injection. The OS eye was separated into a cornea flat mount (panel A, magnified insert shown in panel B) and a retina flat mount (panel C, magnified insert shown in panel D). Staining shows eGFP localized to the cornea endothelium and a few cells staining in the retina. The OD eye was collected whole and processed for cross-sections shown in panel E. Staining shows eGFP localized to the cornea endothelium and not in the retina. Magnified inserts are shown in panels F-G. Panel F shows the cornea endothelium layer. Panel G shows the retina, where the exposure time had to be increased to capture a positive signal not seen in panel E. (green=endogenous eGFP, red=secondary staining using primary antibody to eGFP).

[0027] Figure 5: Figure 5 depicts the in vivo images of a mouse eye after intracameral delivery of AAV6-eGFP. Panel A provides a reference for panel B. Panel B shows the image which demonstrates fluorescence in the cornea from the AAV6-eGFP. Panel C shows the fundus image and panel D shows the image which demonstrates fluorescence in the retina.

[0028] Figure 6: Figure 6 depicts the immunohistochemistry of the same mouse eye shown in Fig. 5. Staining demonstrates that AAV6-eGFP is present in the corneal endothelium, stroma, and ciliary body (green=endogenous eGFP, red=secondary staining using primary antibody to eGFP, blue= DAPI stained nuclei). The white rectangle in panel A indicates the zoomed-in area shown in panel B. The left arrow in panel B indicates the positive corneal stroma layer. The right arrow in panel B indicates the positive corneal endothelium layer.

[0029] **Figure 7:** Figure 7 depicts the *in vivo* images of a mouse eye after intracameral delivery of AAV8-eGFP. Panel A provides a reference for panel B. Panel B shows the image which demonstrates fluorescence in the cornea from the AAV8-eGFP. Panel C shows the fundus image and panel D shows the image which demonstrates fluorescence in the retina.

[0030] **Figure 8:** Figure 8 depicts the immunohistochemistry of the same mouse eye shown in Fig. 7. Staining demonstrates that AAV8-eGFP is present in the corneal endothelium, stroma, and ciliary body (green=endogenous eGFP, red=secondary staining using primary antibody to eGFP, blue= DAPI stained nuclei). The white rectangle in panel A indicates the zoomed-in area shown in panel B. The left arrow in panel B indicates the positive corneal stroma layer. The right arrow in panel B indicates the positive corneal endothelium layer.

[0031] **Figure 9:** Figure 9 depicts the ELISA results of eGFP protein levels from 4 mice (whole eyes) for each of the AAV serotypes, such as AAV5-eGFP, AAV6-eGFP, AAV8-eGFP, delivered by intracameral route. Two mice that received PBS+0.001% pluronic acid were included as controls for each of the AAV serotypes tested. Means with SEM are shown.

[0032] **Figure 10:** Figure 10 is a composite figure that depicts the *in vivo* fluorescence images and immunochemistry results of AAV2-eGFP, AAV5-eGFP, AAV6-eGFP, AAV8-eGFP, and AAV9-eGFP after IC delivery into the mouse eye.

DETAILED DESCRIPTION

[0033] It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only, and are not restrictive of any subject matter claimed.

[0034] Headings are used solely for organizational purposes, and are not intended to limit the invention in any way.

[0035] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the inventions belong. All patents, patent applications, published applications and publications, websites and other

published materials referred to throughout the entire disclosure herein, unless noted otherwise, are incorporated by reference in their entirety for any purpose. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods are described.

[0036] Corneal dystrophy is a term for the heterogeneous group of non-inflammatory bilateral diseases restricted to the cornea. They are grouped by the anatomical location of the pathology within the cornea. Most do not have any manifestations outside of the cornea and they result with corneal opacities and affect visual acuity (see <https://www.cornealdystrophyfoundation.org/what-is-corneal-dystrophy>).

[0037] Anterior corneal dystrophies affect the corneal epithelium and its basement membrane and the superficial corneal stroma. Stromal corneal dystrophies affect the corneal stroma. Posterior corneal dystrophies affect Descemet membrane and the corneal endothelium. The most common posterior corneal dystrophy is Fuchs' corneal endothelial dystrophy.

[0038] The cornea has three major regions that are affected by corneal dystrophies: corneal epithelium, stroma and endothelium. AAV5 targets the corneal endothelium after IC delivery and could be utilized to deliver gene therapy for posterior corneal dystrophies. Both AAV6 and AAV8 can target the corneal stroma, endothelium, and ciliary body after IC delivery and could be utilized to deliver gene therapy for corneal stromal dystrophies and posterior corneal dystrophies. As some anterior corneal dystrophies affect both the epithelium and the superficial corneal stroma, AAV6 and AAV8 could deliver gene therapy to the stroma.

[0039] Table D1 shows corneal dystrophies and certain genes associated therewith ((Klintworth, 2009. Corneal dystrophies. Orphanet J. Rare Dis., 4, 7. doi:10.1186/1750-1172-4-7).

Table D1. Summary of the corneal dystrophies: modes of inheritance, gene loci, genes and the categories of the International Committee for the Classification of Corneal Dystrophies (IC3D) categories.

	Mode of inheritance	Gene locus	Gene	IC3D Category *
SUPERFICIAL CORNEAL DYSTROPHIES				
Meesmann dystrophy	AD	12q13	<i>KRT3</i>	1
Meesmann dystrophy	AD	17q12	<i>KRT12</i>	1
Stocker-Holt dystrophy	AD	17q12	<i>KRT12</i>	1
Granular corneal dystrophy type III (Reis-Bücklers dystrophy)	AD	5q31	<i>TGFB1</i>	1
Thiel-Behnke dystrophy	AD	5q31	<i>TGFB1</i>	1
Thiel-Behnke dystrophy	AD	10q23-q24	Unknown	2
Gelatinous droplike corneal dystrophy (familial subepithelial corneal amyloidosis)	AR	1p32	<i>TACSTD2 (MISI)</i>	1
Subepithelial mucinous corneal dystrophy	AD	Unknown	Unknown	4
Lisch epithelial dystrophy	XR	Xp22.3	Unknown	2
Epithelial recurrent erosion dystrophy	AD	Unknown	Unknown	3
CORNEAL STROMAL DYSTROPHIES				
Macular corneal dystrophy	AR	16q22	<i>CHST6</i>	1
Granular corneal dystrophy type I	AD	5q31	<i>TGFB1</i>	1
Granular corneal dystrophy type II (Avellino dystrophy, combined lattice-granular dystrophy)	AD	5q31	<i>TGFB1</i>	1
Lattice corneal dystrophy type I and variants	AD	5q31	<i>TGFB1</i>	1
Lattice corneal dystrophy type II	AD	9q34	<i>GSN</i>	1
Fleck dystrophy	AD	2q35	<i>PIP5K3</i>	1
Schnyder corneal dystrophy	AD	1p34.1-p35	<i>UBIAD1</i>	1
Posterior amorphous corneal dystrophy	AD	Unknown	Unknown	3
Congenital stromal dystrophy	AD	12q13.2	<i>DCN</i>	1
POSTERIOR DYSTROPHIES				
Fuchs dystrophy (early onset)	AD	1p34.3	<i>COL8A</i>	1
Fuchs dystrophy (late onset)	AD	13pTel-13q12.13	Unknown	2
Fuchs dystrophy (late onset)	AD	18q21.2-q21.32	Unknown	2
Fuchs dystrophy (late onset)	?	20p13-p12	<i>SLC4A11</i>	1
Fuchs dystrophy (late onset)	?	10p11.2	<i>TCF8</i>	1

	Mode of inheritance	Gene locus	Gene	IC3D Category *
Posterior polymorphous dystrophy type 1	AD	20p11.2	Unknown	2
Posterior polymorphous dystrophy type 2	AD	1p34.3-p32.3	<i>COL8A2</i> #	1
Posterior polymorphous dystrophy type 3	AD	10p11.2	<i>TCF8</i>	1
Congenital endothelial dystrophy type 1	AD	20p11.2-q11.2	Unknown	2
Congenital endothelial dystrophy type 2	AR	20p13-p12	<i>SLC4A11</i>	1
X-linked endothelial corneal dystrophy	XR	Unknown	Unknown	2

*Category 1: A well-defined corneal dystrophy in which the gene has been mapped and identified and specific mutations are known.

Category 2: A well-defined corneal dystrophy that has been mapped to 1 or more specific chromosomal loci, but the gene(s) remains to be identified.

Category 3: A well-defined corneal dystrophy in which the disorder has not yet been mapped to a chromosomal locus.

Category 4: A suspected new, or previously documented corneal dystrophy, although the evidence for it, being a distinct entity, is not yet convincing.

[0040] Table D2 is from Moore, C. B. T., Christie, K. A., Marshall, J., & Nesbit, M. A. (2018). Personalised genome editing - The future for corneal dystrophies. *Prog Retin Eye Res*, 65, 147-165. doi:10.1016/j.preteyeres.2018.01.004.

Table D2. List of known corneal dystrophies, including associated inheritance pattern, gene locus and causative genes.

		Inheritance Pattern	Genetic Locus	Gene known	Gene(s) Affected	IC3D Category
Epithelial and Sub-Epithelial Dystrophies	EBMD	Minority of cases, mostly sporadic	5q13	Some cases	<i>TGFBI</i>	Some C1
	ERED	Autosomal Dominant	Unknown	Unknown	N/A	C3
	SMCD	Likely Autosomal Dominant	Unknown	Unknown	Unknown	C4

		Inheritance Pattern	Genetic Locus	Gene known	Gene(s) Affected	IC3D Category
	MECD	Autosomal Dominant	12q13 and 17q12	Yes	<i>KRT3</i> and <i>KRT12</i> (Stocker-Holt variant)	C1
	LECD	X-chromosomal dominant	Xq22.3	Unknown	Unknown	C2
	GDCD	Autosomal Recessive	1q32	Yes	<i>TACSTD2</i> , previously <i>MIS1</i>	C1
Epithelial Stromal Dystrophies	RBCD	Autosomal Dominant	5q13	Yes	<i>TGFB1</i>	C1
	TBCD	Autosomal Dominant	5q13	Yes	<i>TGFB1</i>	C1
	LCD1	Autosomal Dominant	5q13	Yes	<i>TGFB1</i>	C1
	GCD1	Autosomal Dominant	5q13	Yes	<i>TGFB1</i>	C1
	GCD2	Autosomal Dominant	5q13	Unknown	<i>TGFB1</i>	C1
Stromal Dystrophies	MCD	Autosomal Recessive	16q22	Yes	<i>CHST6</i>	C1
	SCD	Autosomal Dominant	1q36	Yes	<i>UBIAD1</i>	C1
	CSCD	Autosomal Dominant	12q21.33	Yes	<i>DCN</i>	C1
	FCD	Autosomal Dominant	2q34	Yes	<i>PIKFYVE</i> , previously <i>PIP5K3</i>	C1
	PACD	Autosomal Dominant	12q21.33	Yes	<i>KERA</i> , <i>LUM</i> , <i>DCN</i> , <i>EPYC</i>	C1
	CCDF	Unknown	Unknown	Unknown	Unknown	C4
	PDCD	Reported AD, similar deposits seen with X-linked ichthyosis	X-linked ichthyosis = Xp22.31	Unknown	<i>STS</i>	C4

		Inheritance Pattern	Genetic Locus	Gene known	Gene(s) Affected	IC3D Category
Descemet's Membrane and Endothelial Dystrophies	FECD	Unknown, reported autosomal dominant	Early onset = 1q34.3-p32 (FECD1) Late onset = 13p34-q12.3 (FECD2), 18q21.2-q21.3 (FECD3), 20p13-q12 (FECD4), 5q33.1-q35.2 (FECD 5), 10p11.2 (FECD 6), 9p24.1-p22.1 (FECD 7), 15q25 (FECD 8)	Some cases	Unknown, <i>TCF4</i> , <i>SLC4A11</i> , Unknown, <i>ZEB1</i> , Unknown, <i>AGBL1</i>	C2 = identified genetic loci, C3 = without known inheritance
	PPCD	Autosomal Dominant	PPCD 1 = 20p11.2-q11.2 PPCD 2 = 1p34.3-p32.3 PPCD 3 = 10p11.2	Unknown Yes Yes	Unknown <i>COL8A2</i> <i>ZEB1</i>	C2 C1 C1
	CHED	Autosomal recessive	20p13	Yes	<i>SLC4A11</i>	C1 (some cases C3)
	XECD	X-chromosomal dominant	Xq25	Unknown	Unknown	C2
Total:	22	Known = 17	Known = 18	Known = 12 Partially known = 4 Unknown = 5		

[0041] Delivering AAVs directly to the eye, for example by intracameral injection, can result in a viral targeting tropism to the cornea. Delivering AAV5 via intracameral injection results in a viral targeting tropism to the cornea endothelium, and not to other ocular structures. This targeted tropism could deliver the therapeutic to the affected structure, while sparing other ocular structures, decreasing the risk of off-target effects. Intracameral delivery of AAV6 or AAV8 also demonstrates targeting to the corneal endothelium. However, both AAV6 and

AAV8 also display tropism to other corneal and anterior structures, as well as the retina, when delivering a gene using the ubiquitous CAG promoter.

[0042] AAV is a small virus consisting of two open reading frames, Rep and Cap, flanked by two 145 base inverted terminal repeats (ITRs). When used for gene therapy, the Rep and Cap open reading frames are removed, and the desired gene, together with a promoter to drive transcription of the desired gene, is inserted between the ITRs.

[0043] CRISPR nucleotides (e.g. gRNA and/or nucleotides coding for Cas proteins) can be packaged between the ITRs, creating a viral vector for targeted delivery of therapeutics. In some embodiments, the CRISPR nucleotide gRNA is packaged with a Cas protein (e.g. Cas9 nuclease) to form a ribonucleoprotein (RNP) complex. However, the AAVs can also be packaged with nucleotides encoding other proteins. AAVs are preferred viral vectors because they can infect both dividing and non-dividing cells, and are associated with a lack of pathogenicity.

[0044] AAV vectors can thus be used to preferentially target certain layers of the cornea. AAV5, for example, specifically targets cornea endothelium. The specificity of AAV vectors reduces the risk for off-target effects of therapeutics that are delivered via the AAV vectors.

[0045] In certain embodiments, the AAV vectors can comprise one or more nucleotide sequences that are complementary to at least one target sequence on a target gene.

[0046] In some embodiments, the AAV vectors can comprise one or more nucleotide acid editing systems. Nucleotide editing systems include, but are not limited to a CRISPR system, an siRNA, an shRNA, an miRNA, an antisense RNA, or an antagomir RNA.

[0047] In certain embodiments, AAV vectors can be used for targeted gene editing or therapy in the eye, preferably the cornea or other affected anterior structures, by delivering one or more nucleotide editing systems directly to the eye.

[0048] In certain embodiments, the AAV vectors can be used for targeted gene therapy in the cornea, by delivering CRISPR complexes targeting genes involved in corneal dystrophies,

such as Fuchs endothelial corneal dystrophy (FECD). FECD is associated with trinucleotide repeat (TNR) expansions in the *transcription factor 4* (*TCF4*) gene. Most of the genetic predisposition for FECD is associated with a TNR in the third intron of the *TCF4* gene. FECD is a condition that affects the cornea of the eye, in particular the endothelium. Corneal dystrophies are also associated with mutations in the *COL8A* gene. Mutations of the *COL8A* gene lead to a Gln455Lys, Gln455Val, or Leu450Trp mutation in the gene product.

[0049] By delivering CRISPR complexes (gRNA plus a Cas protein, or a nucleotide encoding a Cas protein) to the cornea endothelium, the TNRs, or a portion thereof, can be excised from the *TCF4* gene in the corneal endothelium, without affecting the *TCF4* gene in other parts of the eye.

[0050] In certain embodiments, CRISPR complexes are packaged into one or more AAV vectors. The CRISPR complexes may target either the TNRs of the *TCF4* gene, or the mutant alleles of the *COL8A2* gene.

[0051] In certain embodiments, the AAV vectors may be delivered by themselves. In other embodiments, the AAV vectors may be enclosed in a lipid nanoparticle, liposome, non-lipid nanoparticle, or viral capsid for delivery.

Definitions

[0052] In this application, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the singular forms “a,” “an” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise.

[0053] In this application, the use of “or” means “and/or” unless stated otherwise.

[0054] As used herein, the terms “comprises” and/or “comprising” specify the presence of the stated features, integers, steps, operations, elements, and/or components, but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, and/or groups thereof. Furthermore, to the extent that the terms “includes,” “having,” “has,” “with,” “composed,” “comprised” or variants thereof are used in

either the detailed description or the claims, such terms are intended to be inclusive in a manner similar to the term “comprising.”

[0055] As used herein, ranges and amounts can be expressed as “about” a particular value or range. “About” is intended to also include the exact amount. Hence “about 5 percent” means “about 5 percent” and also “5 percent.” “About” means within typical experimental error for the application or purpose intended.

[0056] As used herein, “treatment” refers to any delivery, administration, or application of a therapeutic for a disease or condition. Treatment may include curing the disease, inhibiting the disease, slowing or stopping the development of the disease, ameliorating one or more symptoms of the disease, or preventing the recurrence of one or more symptoms of the disease.

[0057] As used herein, “FECD” refers to Fuchs endothelial corneal dystrophy. FECD includes patients who have the condition, as well as individuals who do not have symptoms, but have a genetic disposition to FECD.

[0058] As used herein, “AAV” refers to an adeno-associated virus. AAV is a non-enveloped virus that is icosahedral, is about 20 to 24 nm long with a density of about 1.40-1.41 g/cc, and contains a single stranded linear genomic DNA molecule approximately 4.7 kb in length. The single stranded AAV genomic DNA can be either a plus strand, or a minus strand. In certain embodiments, the term “AAV” or “AAV vector” refers to an AAV that has been modified so that a therapeutic, such as for example, a CRISPR complex, replaces the Rep and Cap open reading frames between the inverted terminal repeats (ITRs) of the AAV genome.

[0059] As used herein, “AAV serotype” means a sub-division of AAV that is identifiable by serologic or DNA sequencing methods and can be distinguished by its antigenic character.

[0060] As used herein, a “vector” is a composition of matter which comprises an isolated nucleic acid and which can be used to deliver the isolated nucleic acid to the interior of a cell. Vectors include, but are not limited to, linear polynucleotides, polynucleotides associated with ionic or amphiphilic compounds, plasmids, and viruses. The term “vector” includes an

autonomously replicating plasmid or a virus. “Vector” may also include non-plasmid and non-viral compounds which facilitate transfer of nucleic acid into cells, such as, for example, polylysine compounds liposomes, lipid nanoparticles, non-lipid nanoparticles, and the like. Examples of viral vectors include, but are not limited to, adenoviral vectors, adeno-associated virus (AAV) vectors, retroviral vectors, lentiviral vectors, and the like. Preferably, the vector is an AAV vector.

[0061] As used herein, “RNA” refers to a molecule comprising one or more ribonucleotide residues. A “ribonucleotide” is a nucleotide with a hydroxyl group at the 2’ position of the beta-D-ribofuranose moiety. The term “RNA” includes double-stranded RNA, single-stranded RNA, isolated RNA (e.g. partially purified RNA), essentially pure RNA, synthetic RNA, and recombinantly produced RNA. The term “RNA” also refers to modified RNA that differs from naturally-occurring RNA by the addition, deletion, substitution and/or alteration of one or more nucleotides, such as non-naturally occurring nucleotides or chemically synthesized nucleotides or deoxynucleotides.

[0062] As used herein “inhibitory RNA” means a nucleic acid molecule that contains a sequence that is complementary to a target nucleic acid that mediates a decrease in the level or activity of the target nucleic acid. Inhibitory RNA includes, but is not limited to, interfering RNA (iRNA), short hairpin RNA (shRNA), small interfering RNA (siRNA), ribozymes, antagomirs, and antisense oligonucleotides.

[0063] As used herein, “shRNA” refers to an RNA molecule comprising an antisense region, a loop portion, and a sense region, wherein the sense region has complementary nucleotides that base pair with the antisense region to form a duplex stem. Following post-transcriptional processing, the shRNA is converted to siRNA by a cleavage mediated by the enzyme Dicer, which is a member of the RNase III family.

[0064] As used herein, “siRNA” refers to any small RNA molecule capable of inhibiting or down-regulating gene expression by mediating RNA interference in a sequence specific manner.

[0065] As used herein, “antisense RNA” or “antisense oligonucleotides” are short, synthetic pieces of nucleic acid whose sequence is complementary to the mRNA that codes for a protein. Antisense RNA binds to the mRNA and blocks transcription.

[0066] As used herein, an “antagomir” or “antagomir RNA” refers to small synthetic RNA that are complementary to a specific microRNA (miRNA) target, optionally with either mispairing at the cleavage site or one or more base modifications to inhibit cleavage.

[0067] As used herein, “micro RNA” or “miRNA” refers to a single-stranded RNA molecule of about 21-23 nucleotides in length, which regulates gene expression. miRNA molecules are partially complementary to one or more mRNA, and their main function is to down-regulate gene expression.

[0068] As used herein, “TNRs” refers to trinucleotide repeats (i.e. multiple repetitions of three base pairs). The term “TNR expansion” refers to a higher than normal number of TNRs. For example, about 50 or more TNRs in intron 3 of *TCF4* would be considered a TNR expansion.

[0069] As used herein “CRISPR” means a bacterial adaptive immune system known as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeat) sequences.

[0070] As used herein, “guide RNA” and “gRNA” are used interchangeably, and refer to RNA sequences that are directed to a target DNA sequence. The gRNA contains a CRISPR RNA (crRNA) and transactivating crRNA (trRNA or tracrRNA). The crRNA and the trRNA may be associated on a single RNA molecule, referred to as a single guide RNA (sgRNA). Alternatively, the crRNA and trRNA may be disassociated on separate RNA molecules, and form a dual guide RNA (dgRNA). In some embodiments, the gRNA is chemically modified, and comprises one or more modified nucleosides or nucleotides. Modification of nucleosides and nucleotides can include one or more of: i) alteration, e.g. replacement, of one or both of the non-linking phosphate oxygens and/or of one or more of the linking phosphate oxygens in the phosphodiester backbone; ii) alteration, e.g. replacement, of a constituent of the ribose sugar, such as, for example, the 2'-hydroxyl on the ribose sugar; iii) complete replacement of the phosphate moiety with “dephospho” linkers; iv) modification or replacement of a

naturally occurring nucleobase, including with a non-canonical nucleobase; v) replacement or modification of the ribose-phosphate backbone; vi) modification of the 3' end or 5' end of the oligonucleotide, e.g. removal, modification, or replacement of a terminal phosphate group, or conjugation of a moiety, cap, or linker; and vii) modification or replacement of the sugar.

[0071] As used herein, the “guide sequence” refers to an about 20 base-pair sequence within the crRNA or trRNA that is complementary to a target sequence. The guide sequence directs the gRNA to a target sequence for cleavage by a nuclease.

[0072] As used herein, “target sequence” refers to a sequence of nucleic acids, within the genomic DNA of the subject, to which a gRNA directs a nuclease for cleavage of the target sequence. For example, a Cas protein may be directed by a gRNA to a target sequence, where the gRNA hybridizes with the target sequence, and the nuclease cleaves the target sequence. Target sequences include both the positive and negative strands of DNA (i.e. the sequence, and the reverse complement of the sequence). In some embodiments, when the guide sequence is the reverse complement of the target sequence, the guide sequence may be identical to the first 20 nucleotides of the target sequence. As used herein, “target sequence” or “target site” also refers to a genomic nucleic acid sequence that defines a portion of a nucleic acid to which a binding molecule may specifically bind under conditions sufficient for binding to occur.

[0073] As used herein, the term “CRISPR complex” refers to a combination of a gRNA and an endonuclease encoding for a Cas protein (gRNA:Cas endonuclease), or a combination of a gRNA and a Cas protein (gRNA:Cas protein). As used herein, a “ribonucleoprotein” (RNP) refers to a gRNA:Cas protein complex. The CRISPR complexes of the present invention may be directed to and cleave a target sequence either within the TNRs, or flanking the TNRs (5' or 3') of the *TCF4* gene. The CRISPR complexes may also be directed to cleave a target sequence in the *COL8A* gene. As used herein, a “protospacer adjacent motif” or “PAM” refers to a nucleotide sequence that must be adjacent to a target nucleotide sequence. The required PAM depends on the specific CRISPR system used. For example, in the CRISPR/Cas system derived from *Streptococcus pyogenes*, the target DNA must immediately precede a 5'-NGG PAM (where “N” is any nucleobase followed by two guanine nucleobases) for optimal cutting. Although *Streptococcus pyogenes* Cas9 also recognizes the

5'-NAG PAM, it appears to cut less efficiently at these PAM sites. Other Cas9 orthologs (e.g. derived from *Staphylococcus aureus*) require different PAM sequences.

[0074] As used herein, “indels” means insertion/deletion mutations that consist of a number of nucleotides that are either inserted or deleted at the site of double-stranded breaks (DSBs) in the nucleic acid of the DNA.

[0075] As used herein, “excision fragment” or “excision fragments” refers to deletions of a consecutive number of nucleotides (such as TNRs) that may occur when two or more gRNA are used together with a Cas mRNA or Cas protein.

[0076] As used herein, “promoter” means a DNA sequence recognized by the synthetic machinery of the cell, or introduced synthetic machinery, required to initiate specific transcription of a polynucleotide sequence. Preferred are promoters that are operable for AAV vectors, preferably AAV5, AAV6, and/or AAV8, and tissue specific promoters, preferably specific for the eye, more preferably specific for the cornea, and most preferably specific for the endothelium of the cornea. AAV promoters include, for example, an AAV p5 promoter. Promoters include, but are not limited to, CAG, SYN1, CMV, NSE, CBA, PDGF, SV40, RSV, LTR, SV40, dihydrofolate reductase promoter, beta-actin promoter, PGK, EF1alpha, GRK, MT, MMTV, TY, RU486, RHO, RHOK, CBA, chimeric CMV-CBA, MLP, RSV, ubiquitin promoters, actin promoters, tubulin promoters, immunoglobulin promoters, functional fragments thereof, etc. In AAV packaged with heterologous DNA, a promoter normally associated with heterologous nucleic acid can be used, or a promoter normally associated with the AAV vector, or a promoter not normally associated with either, can be used.

[0077] As used herein, “constitutive promoter” is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell under most or all physiological conditions of the cell. Examples of constitutive promoters include, but are not limited to, cytomegalovirus immediate early promoter (CMV), simian virus (SV40) promoter, adenovirus major late (MLP) promoter, Rous sarcoma virus (RSV) promoter, elongation factor-alpha (EF1a)

promoter, ubiquitin promoters, actin promoters, tubulin promoters, immunoglobulin promoters, functional fragments thereof, or combinations thereof.

[0078] As used herein, “inducible promoter” is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell substantially only when an inducer which corresponds to the promoter is present in the cell. Examples of inducible promoters include, but are not limited to, those inducible by heat shock, light, chemicals, peptides, metals, steroids, antibiotics, or alcohol. In some embodiments the promoter may be tissue specific, such as a promoter specific for expression in the cornea, e.g. the corneal endothelium.

[0079] As used herein, a “tissue specific promoter” is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a cell substantially only if the cell is a cell of the tissue type corresponding to the promoter. Tissue specific promoters include, but are not limited to, CMV, CBA, RHO, and RHOK.

[0080] As used herein, a “promoter/regulatory sequence” means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. This sequence may be the core promoter sequence, or it may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product.

[0081] As used herein, “under transcriptional control” or “operably linked” means that the promoter is in the correct location and orientation in relation to a polynucleotide to control initiation of transcription by RNA polymerase and expression of the polynucleotide. These include promoters, a 3' UTR, or a 5' UTR. The promoter may be recognized by RNA polymerase III (Pol III), such as, but limited to, U6 and H1 Pol III promoters. The Pol III promoters may be, for example, mouse or human.

[0082] As used herein, “gene editing” or “nucleic acid editing” refers to modification of the nucleic acid sequence of a target gene.

[0083] As used herein, “nucleic acid editing system” or “gene editing system” refers to a method that can be used for performing gene editing or nucleic acid editing. Nucleic acid editing systems and gene editing systems include CRISPR systems, and interfering RNAs.

[0084] As used herein, “delivery system” refers to materials used to deliver nucleic acids to target cells. Such materials may include viral vectors such as AAV vectors and pharmaceutically acceptable ingredients.

[0085] As used herein, “modulation” or “modification” includes decreasing or inhibiting expression or function, of for example, a gene or protein, as well as increasing expression or function, of for example, a gene or protein. As used herein, “modulation” or “modification” also includes complete restoration of gene function, which includes replacing mutated part(s) of a gene or replacing the mutant gene with a wild-type version.

[0086] As used herein, “down-regulating” or “down-regulation” means a reduction in expression or transcription of a target nucleotide sequence. Down-regulation may be partial or temporary reduction in the expression or transcription of a target nucleotide sequence. Down-regulation may be a complete elimination of the expression or transcription of a target nucleotide sequence.

[0087] As used herein, “knockdown” refers to a partial or temporary reduction in expression or transcription of a target nucleotide sequence. This may be accomplished by administering a complementary nucleotide sequence that binds to the target sequence. Knockdown can be elicited by antisense oligonucleotides, siRNA, and the like.

[0088] As used herein, “knockout” refers to complete elimination of the expression or transcription of a target nucleotide sequence. Knockout may be elicited, for example, by use of a CRISPR system to cleave the target nucleotide sequence out of the target gene.

[0089] As used herein, non-homologous end joining (NHEJ) is a DNA repair mechanism which is a re-ligation of break ends after cleavage of a target nucleotide sequence.

[0090] As used herein, “homologous repair/homology directed repair (HR/HDR)” refers to DNA repair which is a process of homologous recombination where a DNA template is used to provide the homology necessary for precise repair of a double-strand break. The repair may consist of insertions of desired sequences, or modification of the target sequence.

[0091] As used herein, “repair template” refers to the DNA template used in HR/HDR.

[0092] As used herein, “subject” means a living organism. Preferably, a subject is a mammal, such as a human, non-human primate, rodent, or companion animal such as a dog, cat, cow, pig, etc.

Modulation of gene expression

[0093] Gene expression can be modulated by administering to a subject in need thereof a composition comprising a nucleotide editing system.

[0094] In one embodiment, modulating expression of a target gene comprises administering to the subject a composition, wherein the composition comprises a nucleic acid editing system comprising at least one nucleotide sequence that is complementary to at least one allele on a target gene associated with corneal dystrophies. In certain embodiments, the at least one nucleotide sequence that is complementary to at least one allele on a target gene is selected from an siRNA, an shRNA, an miRNA, an antisense RNA, or an antagomir RNA.

Administration of the composition

[0095] In certain embodiments, the composition is administered by itself.

[0096] In preferred embodiments, the composition comprises an adeno-associated virus (AAV) vector, or a nucleotide sequence or portion thereof encoding an AAV vector.

AAV

[0097] Adeno-associated virus (AAV) is a small, replication-deficient parvovirus. AAV is about 20-24 nm long, with a density of about 1.40-1.41 g/cc. AAV contains a single-stranded linear genomic DNA molecule approximately 4.7 kb in length. The single-stranded AAV genomic DNA can be either a plus strand, or a minus strand. AAV contains two open

reading frames, Rep and Cap, flanked by two 145 base inverted terminal repeats (ITRs). AAVs contain a single intron. Cis-acting sequences directing viral DNA replication (Rep), encapsidation/packaging and host cell chromosome integration are contained within the ITRs. Three AAV promoters, p5, p19, and p40 (named for their relative map locations) drive the expression of the two AAV internal open reading frames encoding rep and cap genes. The p5 and p19 are the rep promoters. When coupled with the differential splicing of the single AAV intron, the two rep promoters result in the production of four rep proteins (rep 78, rep 68, rep 52, and rep 40) from the rep gene. The rep proteins have multiple enzymatic properties that are responsible for replicating the viral genome. The cap gene is expressed from the p40 promoter, and encodes the three capsid proteins VP1, VP2, and VP3. Alternative splicing and non-consensus translational start sites are responsible for the production of the three related capsid proteins. A single polyadenylation site is located at map position 95 of the AAV genome. Muzyczka reviews the life cycle and genetics of AAV (Muzyczka, *Current Topics in Microbiology and Immunology*, 158:97-129 (1992)).

[0098] AAV infection is non-cytopathic in cultured cells. Natural infection of humans and other animals is silent and asymptomatic (does not cause disease). Because AAV infects many mammalian cells, there is the possibility of targeting many different tissues *in vivo*. In addition to dividing cells, AAV transduces slowly dividing and non-dividing cells, and can persist essentially for the lifetime of those cells as a transcriptionally active nuclear episome (i.e. extrachromosomal element). The AAV proviral genome is infective as cloned DNA in plasmids, which makes construction of recombinant genomes possible. Moreover, because the signals directing AAV replication, genome encapsidation, and integration are all contained within the ITRs of the AAV genome, some or all of the approximately 4.3 kb of the genome, encoding replication and structural capsid proteins (rep-cap) are contained within the ITRs of the AAV genome, and can be replaced with heterologous DNA, such as a gene cassette containing a promoter, a DNA of interest, and a polyadenylation signal. The rep and cap proteins may be provided in trans.

[0099] Several AAV serotypes have been identified, differing in their tropism (type of cell that they infect). Serotype AAV1 shows tropism to the following tissues: CNS; heart; retinal pigment epithelium (RPE); and skeletal muscle. Serotype AAV2 shows tropism to the following tissues: CNS; kidney; photoreceptor cells; and RPE. Serotype AAV3 shows

tropism mainly to the heart and liver. Serotype AAV4 shows tropism to the following tissues: CNS; lung; and RPE. Serotype AAV5 shows tropism to the following tissues: CNS; lung; photoreceptor cells; and RPE. Serotype AAV6 shows tropism to the following tissues: lung; and skeletal muscle. Serotype AAV7 shows tropism to the following tissues: liver; and skeletal muscle. Serotype AAV8 shows tropism to the following tissues: CNS; heart; liver; pancreas; photoreceptor cells; RPE; and skeletal muscle. Serotype AAV9 shows tropism for the following tissues: CNS; heart; liver; lung; and skeletal muscle. The tropism of AAV viruses may be related to the variability of the amino acid sequences of the capsid protein, which may bind to different functional receptors present on different types of cells.

[00100] Depending on the promoter included in the heterologous DNA cassette, it may be possible to target specific tissues in the eye. Modifying the capsid proteins may also enable specific infectivity of certain tissues or cells. In one embodiment, an AAV containing an Anc80 or Anc80L65 capsid protein is used for delivery of therapeutics directly to specific tissues in the eye. In some embodiments, the AAV viral particle comprises an AAV1, AAV2, AAV3, AAV4, AAV5, AAV6 (e.g., a wild-type AAV6 capsid, or a variant AAV6 capsid such as ShH10, as described in U.S. PG Pub. 2012/0164106), AAV7, AAV8, AAVrh8, AAVrh8R, AAV9 (e.g., a wild-type AAV9 capsid, or a modified AAV9 capsid as described in U.S. PG Pub. 2013/0323226), AAV10, AAVrh10, AAV11, AAV12, a tyrosine capsid mutant, a heparin binding capsid mutant, an AAV2R471A capsid, an AAVAAV2/2-7m8 capsid, an AAV DJ capsid (e.g., an AAV-DJ/8 capsid, an AAV-DJ/9 capsid, or any other of the capsids described in U.S. PG Pub. 2012/0066783), AAV2 N587A capsid, AAV2 E548A capsid, AAV2 N708A capsid, AAV V708K capsid, goat AAV capsid, AAV1/AAV2 chimeric capsid, bovine AAV capsid, mouse AAV capsid, rAAV2/HBoV1 capsid, or an AAV capsid described in U.S. Pat. No. 8,283,151 or International Publication No. WO/2003/042397. In some embodiments, the AAV viral particle comprises an AAV capsid comprising an amino acid substitution at one or more of positions R484, R487, K527, K532, R585 or R588, numbering based on VP1 of AAV2. In further embodiments, a AAV particle comprises capsid proteins of an AAV serotype from Classes A-F. In some embodiments, the rAAV viral particle comprises an AAV serotype 2 capsid. In further embodiments, the AAV serotype 2 capsid comprises AAV2 capsid protein comprising a R471A amino acid substitution, numbering relative to AAV2 VP1. In some embodiments, the vector comprises AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAVrh8, AAVrh8R, AAV9,

AAV10, AAVrh10, AAV11, AAV12, AAV2R471A, AAV DJ, a goat AAV, bovine AAV, or mouse AAV serotype inverted terminal repeats (ITRs). In some embodiments, the vector comprises AAV serotype 2 ITRs. In some embodiments, the AAV viral particle comprises one or more ITRs and capsid derived from the same AAV serotype. In other embodiments, the AAV viral particle comprises one or more ITRs derived from a different AAV serotype than the capsid of the rAAV viral particles. In some embodiments, the rAAV viral particle comprises an AAV2 capsid, and wherein the vector comprises AAV2 ITRs. In further embodiments, the AAV2 capsid comprises AAV2 capsid protein comprising a R471A amino acid substitution, numbering relative to AAV2 VP1 (see US Patent Publication 2017/0304465).

[00101] It has recently been shown that including a human rhodopsin kinase (hGRK1) promoter in an AAV5 vector results in rod- and cone-specific expression in the primate retina (Boye, et al., *Human Gene Therapy*, 23:1101-1115 (October 2012) (DOI: 10.1089/hum.2012.125)).

[00102] It has also recently been shown that AAV virions with altered capsid proteins may impart greater tissue specific infectivity. For example, AAV6 with a variant capsid protein shows increased infectivity of retinal cells, compared to wild-type AAV capsid protein (US 8,663,624). A variant capsid protein comprising a peptide insertion between two adjacent amino acids corresponding to amino acids 570 ad 611 of VP1 of AAV2, or the corresponding position in a capsid protein of another AAV serotype, confers increased infectivity of retinal cells, compared to wild-type AAV (US 9,193,956).

Expression of protein in a cornea

[00103] To express specific proteins in a cornea, AAV vectors packaged with either an endonucleotide encoding the desired protein, or AAV vectors packaged with the desired protein may be delivered or administered directly to the eye. Proteins can include, for example, CRISPR associated (Cas) proteins, or marker proteins (e.g. green fluorescent protein (GFP or eGFP)).

[00104] In certain embodiments, the AAV vectors may be delivered without being enclosed in any particle or lipid vessels. In other embodiments, the AAV vectors may be enclosed in a lipid nanoparticle, liposome, non-lipid nanoparticle, or viral capsid for delivery.

[00105] In some embodiments, the compositions and/or the AAV vectors can be delivered directly to the eye. The composition and/or AAV vector may be administered to the anterior chamber of the eye, the posterior chamber of the eye, the cornea, or the vitreous chamber of the eye. In preferred embodiments, the AAV vectors are administered directly to the aqueous humor of the anterior chamber, which is in contact with the cornea. More than one AAV vector such as a dual AAV vector system may be used for the purpose of modulating gene expression as defined in the present invention.

[00106] As explained above, there are several AAV serotypes, each exhibiting tropism for certain types of tissue. Although the AAV serotype used is not particularly limited, the AAV5, AAV6, and AAV8 serotypes are preferred AAV vectors for targeting corneal and anterior tissues in the eye.

[00107] To test the viral tropism of different AAV serotypes in the present invention, several serotypes were packaged with a nucleotide sequence encoding green fluorescent protein (GFP or eGFP). These AAV-eGFP complexes were delivered intracamerally into the eye. The fluorescence of the GFP could be measured in vivo, showing the localization of the AAV-GFP. The localization of the GFP could also be assessed by performing immunohistochemistry on sections of the eye. The viral tropism of AAV5, as indicated by immunohistochemical staining, was localized to the corneal endothelium. The viral tropism of AAV6 was localized to the cornea endothelium, stroma and endothelium, and ciliary body, with some targeting to retinal cells. The viral tropism of AAV8 was localized to cornea endothelium and stroma, and ciliary body, with some targeting to retinal cells. The viral tropism of AAV2 and AAV9 was localized to both the posterior and anterior segments of the eye after IC administration, with greater expression in the posterior segment than the anterior segment.

[00108] The results show that AAV5, AAV6, and AAV8 show selective tropism for corneal tissues. When selective targeting to the cornea endothelium is desired, use of AAV5 is

preferred. Use of other AAV serotypes (e.g. AAV2), which are less tissue selective, may lead to unwanted off-target effects.

[00109] In certain embodiments, the AAV vectors may be delivered by themselves. In other embodiments, the AAV vectors may be enclosed in a lipid nanoparticle, liposome, non-lipid nanoparticle, or viral capsid for delivery.

[00110] In some embodiments, the AAV vectors can be delivered directly to the eye. The AAV vector may be administered to the anterior chamber of the eye, the posterior chamber of the eye, the cornea, or the vitreous chamber of the eye. In certain embodiments, the AAV vectors can be administered to the corneal stroma, corneal limbus, onto the epithelial surface of the cornea, or onto the endothelial membrane of the cornea. In preferred embodiments, the AAV vectors are administered directly to the aqueous humor of the anterior chamber which is in direct contact with the corneal endothelium.

Gene targeting using CRISPR complexes

[00111] In certain embodiments, a CRISPR complex is used to modify a specific nucleotide sequence of the DNA of a gene. The specific nucleotide sequence of the DNA of the gene is the “target sequence.”

[00112] A CRISPR complex is a combination of a gRNA and an endonuclease encoding for a Cas protein (gRNA:Cas endonuclease), or a combination of a gRNA and a Cas protein (gRNA:Cas protein).

[00113] The gRNA comprises RNA sequences that are directed to a target DNA sequence. The gRNA contains a CRISPR RNA (crRNA) and transactivating crRNA (trRNA or tracrRNA). The crRNA and the trRNA may be associated on a single RNA molecule, referred to as a single guide RNA (sgRNA). Alternatively, the crRNA and trRNA may be disassociated on separate RNA molecules, and form a dual guide RNA (dgRNA). The gRNA can be targeted to either the positive or negative strand of the DNA.

[00114] The gRNA guides the Cas component (i.e. endonuclease encoding a Cas protein, or a Cas protein) to the target sequence. The gRNA is complementary to, and hybridizes with,

the target sequence, or the reverse complement of the target sequence. In some embodiments, the gRNA sequence is 100% complementary or identical to the target sequence. Preferably, the degree of complementarity or identity between a guide sequence of a gRNA and its corresponding target sequence is at least about 50% or greater. For example, the degree of complementarity or identity may be about 50%, 55%, 60%, 65%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%.

[00115] In some embodiments, the gRNA is chemically modified, and comprises one or more modified nucleosides or nucleotides. Modification of nucleosides and nucleotides can include one or more of: i) alteration, e.g. replacement, of one or both of the non-linking phosphate oxygens and/or of one or more of the linking phosphate oxygens in the phosphodiester backbone (e.g. phosphorothioate or boranophosphate linkages); ii) alteration, e.g. replacement, of a constituent of the ribose sugar, such as, for example, 2'-O-methyl and/or 2'-fluoro and/or 4-thio modifications; iii) complete replacement of the phosphate moiety with "dephospho" linkers; iv) modification or replacement of a naturally occurring nucleobase, including with a non-canonical nucleobase; v) replacement or modification of the ribose-phosphate backbone; vi) modification of the 3' end or 5' end of the oligonucleotide, e.g. removal, modification, or replacement of a terminal phosphate group, or conjugation of a moiety, cap, or linker; vii) modification or replacement of the sugar; and viii) locked or unlocked nucleic acids. Other modifications include pseudouridine, 2-thiouridine, 4-thiouridine, 5-azauridine, 5-hydroxyuridine, 5-aminouridine 5-methyluridine, 2-thiopseudouridine, 4-thiopseudouridine, 5-hydroxypseudouridine, 5-methylpseudouridine, 5-aminopseudouridine, pseudoisocytidine 5-methylcytidine N-4-methylcytidine, 2-thiocytidine, 5-azacytidine 5-hydroxycytidine, 5-aminocytidine, N-4-methylpseudoisocytidine, 2-thiopseudoisocytidine, 5-hydroxypseudoisocytidine, 5-aminopseudoisocytidine, 5-methylpseudoisocytidine, N-6-methyladenosine, 7-deazaadenosine, 6-thioguanosine, 7-deazaguanosine, 8-azaguanosine, 6-thio-7-deazaguanosine, 6-thio-8-azaguanosine, 7-deaza-8-azaguanosine, and 6-thio-7-deaza-8-azaguanosine.

[00116] In some embodiments the Cas component comprises Type-I, Type-II, or Type-III components. In certain embodiments, the Cas component is a nuclease. In some embodiments the Cas nuclease is Cas9 or Cpf1. Preferably the Cas nuclease is Cas9. In some embodiments, the gene-editing molecule is a Cas protein (e.g. Cpf1, CasX, CasY,

C2C2, Cas1, Cas1B, Cas2, Cas3, Cas4, Cas5, Cas5e (CasD), Cas6, Cas6e, Cas6f, Cas7, Cas8a1, Cas8a2, Cas8b, Cas8c, Cas9 (Csn1 or Csx12), Cas10, Cas10d, CasF, CasG, CasH, Csy1, Csy2, Csy3, Cse1 (CasA), Cse2 (CasB), Cse3 (CasE), Cse4 (CasC), Csc1, Csc2, Csa5, Csn2, Csm2, Csm3, Csm4, Csm5, Csm6, Cmr1, Cmr3, Cmr4, Cmr5, Cmr6, Csb1, Csb2, Csb3, Csx17, Csx14, Csx10, Csx16, CsaX, Csx3, Csx1, Csx15, Csf1, Csf2, Csf3, Csf4, Cul966, or homologs or modified versions thereof). In some embodiments, the Cas protein is a Cas9 protein (e.g., wild-type Cas9, a Cas9 nickase, a dead Cas9 (dCas9), or a split Cas9). In some embodiments, the Cas9 protein is a *Streptococcus pyogenes* Cas9 protein or *Staphylococcus aureus* Cas9 protein.

[00117] Once guided to the target sequence, the Cas nuclease cleaves the target sequence. This leads to double-stranded breaks in the DNA, or single-strand breaks if a nickase enzyme is used. Double-stranded breaks in the DNA can be repaired via non-homologous end joining (NHEJ), which is re-ligation of the break ends. NHEJ can produce indel mutations. Alternatively, the DNA may be repaired via homologous repair (HR) or homology-directed repair (HDR). HR and HDR generate precise, defined modifications at the target locus in the presence of an exogenously introduced repair template. In certain embodiments, the repair template contains a nucleotide sequence encoding a desirable mutation on a target gene, and the nucleotide sequence is inserted at the target locus of the gene.

[00118] Some of the sequences disclosed herein include the following lists (*see* WO 2017/185054). SEQ ID NOs: 1-93 are target sequences 5' of the TNRs in intron 3 of the *TCF4* gene. SEQ ID NOs: 94-190 are target sequences 3' of the TNRs in intron 3 of the *TCF4* gene. SEQ ID NOs: 191-1063 are target sequences for the wild type *COL8A2* gene. SEQ ID NOs: 1064-1069 are target sequences for the *COL8A2* Gln455Lys mutation. SEQ ID NOs: 1070-1075 are target sequences for the *COL8A2* Gln455Ala mutation. SEQ ID NOs: 1076-1084 are target sequences for the *COL8A2* Leu450Trp mutation.

[00119] Table A shows the sequences for SEQ ID NOs: 1085-1088 (*see* Exemplary sequences from WO 2017/185054).

[00120] The guide RNA and Cas components (i.e. the CRISPR complexes) are packaged into AAV vectors for delivery to a subject. In certain embodiments, the AAV vectors may be delivered by themselves. In other embodiments, the AAV vectors may be enclosed in a lipid nanoparticle, liposome, non-lipid nanoparticle, or viral capsid for delivery.

[00121] In some embodiments, the AAV vectors can be delivered directly to the eye. The AAV vector may be administered to the anterior chamber of the eye, the posterior chamber of the eye, the cornea, or the vitreous chamber of the eye. In certain embodiments, the AAV vectors can be administered to the corneal stroma, corneal limbus, onto the epithelial surface of the cornea, or onto the endothelial membrane of the cornea. In preferred embodiments, the AAV vectors are administered directly to the aqueous humor of the anterior chamber which is in direct contact with the corneal endothelium.

TCF4 gene targeting

[00122] The *TCF4* gene is located on chromosome 18. The cytogenic location is 18q21.2 (the long arm of chromosome 18 at position 21.2). The molecular location is on base pairs 55,222,311 to 55,635,993 on chromosome 18 (Homo sapiens Annotation Release 109, GRCh38.p12 (NCBI)).

[00123] The target sequence may be within or flanking the TNRs in the *TCF4* gene. A Cas nuclease is guided to the target sequence. In some embodiments, the Cas nuclease may be guided to a target sequence within the TNRs of the *TCF4* gene. In other embodiments, the Cas nuclease may be guided to a target sequence flanking the TNR. For example, the Cas nuclease may be directed to a target sequence 5' of the TNRs. Or the Cas nuclease may be directed to a target sequence 3' of the TNRs. In some embodiments, the Cas protein may be directed by two or more gRNAs to two target sequences flanking the TNRs. In some embodiments, the Cas nuclease may be directed by two or more gRNAs to two target sequences, wherein one is within the TNRs of the *TCF4* gene, and the other flanks the TNRs of the *TCF4* gene. Target sequences for the *TCF4* gene are chosen from SEQ ID NOs: 1-190. SEQ ID NOs: 1-93 are target sequences 5' of the TNRs in intron 3 of the *TCF4* gene. SEQ ID NOs: 94-190 are target sequences 3' of the TNRs in intron 3 of the *TCF4* gene. Guide sequences for the *TCF4* gene are chosen from SEQ ID NOs: 1089-1278. (see Sequence Listing)

[00124] The one or more gRNA comprise a guide sequence that is complementary to a target sequence in the *TCF4* gene, or the reverse complement of a target sequence in the *TCF4* gene. In some embodiments, the gRNA sequence is 100% complementary or identical to the target sequence. Preferably, the degree of complementarity or identity between a guide sequence of a gRNA and its corresponding target sequence is at least about 50% or greater. For example, the degree of complementarity or identity may be about 50%, 55%, 60%, 65%, 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100%.

[00125] In some embodiments, one gRNA is used. In other embodiments, a combination of two or more gRNA are used. In certain embodiments, a gRNA targeting a sequence 5' of the TNRs is used in combination with a gRNA that targets a sequence 3' to the TNRs, in order to excise the TNRs of the *TCF4* gene. In some embodiments, a gRNA complementary to a target sequence chosen from SEQ ID NOs: 1-93 is used together with a gRNA complementary to a target sequence chosen from SEQ ID NOs: 94-190. Table 1 shows target sequences and corresponding guide sequences (*from* Ex. 1 of WO 2017/185054). Table 2 shows combinations of guide sequences (*From* Ex. 1 of WO 2017/185054). (*see* Exemplary sequences from WO 2017/185054)

[00126] In embodiments wherein the CRISPR complex includes an endonuclease encoding the protein, the endonuclease may be operably linked to one or more transcriptional or translational control sequences. In certain embodiments, the endonuclease is operably linked to one or more promoters. The promoter may be constitutive, inducible, or tissue-specific. Examples of constitutive promoters include, but are not limited to, cytomegalovirus immediate early promoter (CMV), simian virus (SV40) promoter, adenovirus major late (MLP) promoter, Rous sarcoma virus (RSV) promoter, elongation factor- α (EF1 α) promoter, ubiquitin promoters, actin promoters, tubulin promoters, immunoglobulin promoters, functional fragments thereof, or combinations thereof. Examples of inducible promoters include, but are not limited to, those inducible by heat shock, light, chemicals, peptides, metals, steroids, antibiotics, or alcohol. In some embodiments the promoter may be tissue specific, such as a promoter specific for expression in the cornea, e.g. the corneal endothelium.

[00127] In some embodiments, the nucleotide sequence encoding the gRNA may be operably linked to at least one transcriptional or translational control sequences. These include promoters, a 3' UTR, or a 5' UTR. The promoter may be recognized by RNA polymerase III (Pol III), such as, but limited to, U6 and H1 Pol III promoters. The Pol III promoters may be, for example, mouse or human.

[00128] In certain embodiments, one or more gRNA are packaged in AAV vectors, in combination with either an endonuclease sequence encoding a Cas protein, or a Cas protein (e.g. Cas9) (i.e. CRISPR complexes). The AAV serotype used is not particularly limited. Preferably, the AAV vectors are of the AAV5, AAV6, or AAV8 serotype.

[00129] The AAV-CRISPR complexes can be delivered directly into the eye via intracameral or intrastromal injection. In certain embodiments, the AAV vectors may be delivered by themselves. In other embodiments, the AAV vectors may be enclosed in a lipid nanoparticle, liposome, non-lipid nanoparticle, or viral capsid for delivery.

[00130] In some embodiments, the AAV vectors can be delivered directly to the eye. The AAV vector may be administered to the anterior chamber of the eye, the posterior chamber of the eye, the cornea, or to the vitreous chamber of the eye. In certain embodiments, the AAV vectors can be administered to the corneal stroma, corneal limbus, onto the epithelial surface of the cornea, or onto the endothelial membrane of the cornea. In preferred embodiments, the AAV vectors are administered directly to the aqueous humor of the anterior chamber which is in direct contact with the corneal endothelium.

COL8A2 gene targeting

[00131] Mutations in the *COL8A2* gene, and thus the mutations in the gene products, can also be treated with the methods and compositions described herein. This can be done by developing CRISPR complexes that target specific sequences in the *COL8A2* gene that lead to the mutations.

[00132] In some embodiments, a CRISPR complex can be used to excise a target mutant nucleotide sequence on the *COL8A2* gene, and excise a nucleotide sequence of the DNA encoding a mutated gene product. The DNA may then be repaired with the process of NHEJ,

leading to the generation of indels and the loss of the mutant allele. In other embodiments, use of the CRISPR complexes can be done together with either an exogenous template for HR/HDR, or using the endogenous normal allele as a template for HR/HDR, resulting in correction of the nucleic acid mutation that leads to the amino acid mutation in the alpha 2 subunit of COL8. Mutations that can be corrected include: the Gln455Lys mutation, caused by the c.1364C>A nucleotide change; the Gln455Val mutation caused by the c.1363-1364CA>GT nucleotide changes; or the Leu450Trp mutation caused by the c.1349T>G nucleotide change.

[00133] Target sequences for the *COL8A2* gene can be selected using the NCBI Reference Sequence NM_005202.3 of transcript variant 1 of the *COL8A2* gene. This sequence does not contain mutations at positions 455 and 450 in the amino acid sequence of the COL8 gene product, and may be considered the “wild type” *COL8A2* gene sequence. Target sequences can be selected between Chr1:36097532-36100270 (hg38). Target sequences for the *COL8A2* gene are selected from SEQ ID NOs: 191-1063. Target sequences for the wild type *COL8A2* gene are shown in Table 3. Guide sequences complementary to these target sequences can be developed to target the *COL8A2* gene.

[00134] Target sequences to the mutant alleles can also be developed, based on the differences in the nucleotide sequences for the mutant alleles. Table 4 shows target sequences specific for the Gln155Lys mutation, caused by the c.1364C>A nucleotide change (SEQ ID NOs: 1064-1069). Table 5 shows target sequences specific for the Gln455Val mutation, caused by the c.1363-1364CA>GT nucleotide changes (SEQ ID NOs: 1070-1075). Table 6 shows target sequences specific for Leu450Trp mutation, caused by the c.1349T>G nucleotide change (SEQ ID NOs: 1076-1084). The mutant alleles could be targeted using gRNA comprising guide sequences complementary to the target sequences, or comprising guide sequences complementary to the reverse complement of the target sequences.

[00135] In certain embodiments, one or more gRNA are packaged in AAV vectors, in combination with either an endonuclease sequence encoding a Cas protein, or a Cas protein (e.g. Cas9) (i.e. CRISPR complexes). The AAV serotype used is not particularly limited. Preferably, the AAV vectors are of the AAV5, AAV6, or AAV8 serotype.

[00136] The AAV-CRISPR complexes can be delivered directly into the eye via intracameral or intrastromal injection. In certain embodiments, the AAV vectors may be delivered by themselves. In other embodiments, the AAV vectors may be enclosed in a lipid nanoparticle, liposome, non-lipid nanoparticle, or viral capsid for delivery.

[00137] In some embodiments, the AAV vectors can be delivered directly to the eye. The AAV vector may be administered to the anterior chamber of the eye, the posterior chamber of the eye, or the cornea. In certain embodiments, the AAV vectors can be administered to the corneal stroma, corneal limbus, onto the epithelial surface of the cornea, or onto the endothelial membrane of the cornea. In preferred embodiments, the AAV vectors are administered directly to the aqueous humor of the anterior chamber which is in direct contact with the corneal endothelium.

Exemplary embodiments

[00138] In certain embodiments, the mutant allele is encoded by a target sequence on the target gene.

[00139] In some embodiments, at least one nucleotide sequence that is complementary to at least one mutant allele on a target gene hybridizes to a target sequence on the target gene in a cell in the subject.

[00140] In certain embodiments the target gene is *TCF4* or *COL8A2*.

[00141] In some embodiments, at least one target sequence is selected from the group consisting of SEQ ID NOs: 1-1084.

[00142] In some embodiments, at least one target sequence is specific to the *TCF4* gene, and the target sequence is selected from SEQ ID NOs: 1-190.

[00143] In some embodiments, the target sequence is specific to the *COL8A2* gene and the target sequence is selected from SEQ ID NOs: 191-1084

[00144] In some embodiments, the nucleic acid editing system is a CRISPR system, an siRNA, an shRNA, an miRNA, an antisense RNA, or an antagomir RNA.

[00145] In some embodiments, the nucleic acid editing system is a CRISPR system.

[00146] In some embodiments, the nucleic acid editing system is a CRISPR-Cas system.

[00147] In some embodiments, the CRISPR-Cas system comprises a nucleotide sequence encoding a CRISPR-associated (Cas) gene and a nucleotide sequence encoding a guide RNA (gRNA).

[00148] In some embodiments, the Cas gene encodes a Cas protein.

[00149] In some embodiments, the Cas protein encoded by the Cas gene is a Cas nuclease.

[00150] In some embodiments, the Cas nuclease is Cas9.

[00151] In some embodiments, the guide RNA comprises a CRISPR RNA (crRNA) and a trans-activating crRNA (tracrRNA or trRNA).

[00152] In some embodiments, the guide RNA is a single guide RNA (sgRNA), and both the crRNA and the tracrRNA are combined on one guide RNA molecule.

[00153] In some embodiments, the guide RNA is a double guide RNA (dgRNA), and the crRNA and the tracrRNA are on separate RNA molecules, used at the same time, but not combined.

[00154] In some embodiments, the CRISPR-Cas system is a CRISPR-Cas9 system.

[00155] In some embodiments, the crRNA and tracrRNA form a complex with the nucleotide sequence encoding Cas9 nuclease.

[00156] In some embodiments, the nucleotide sequence that is complementary to at least one mutant allele is a gRNA.

[00157] In some embodiments, at least one guide RNA comprises a crRNA sequence that is complementary to at least one target sequence selected from SEQ ID NOs: 1-1084.

[00158] In some embodiments, at least one guide RNA comprises a guide sequence selected from the group consisting of SEQ ID NOs: 1089-1278.

[00159] In some embodiments, the delivery system, vector, gene editing system, or composition further comprises a repair template.

[00160] In some embodiments, the repair template is selected from the group consisting of a DNA repair template, an mRNA repair template, an siRNA repair template, an miRNA repair template, and an antisense oligonucleotide repair template.

[00161] In some embodiments, the AAV vector serotype is selected from the group consisting of AAV1, AAV2, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, AAVrh10.

[00162] In some embodiments, the AAV vector serotype is AAV5, AAV6, or AAV8.

[00163] In some embodiments, the AAV vector serotype is AAV5.

[00164] In some embodiments, the AAV vector serotype is AAV6.

[00165] In some embodiments, the AAV vector serotype is AAV8.

[00166] In some embodiments, the delivery system, vector, nucleotide or gene editing system, or composition further comprises a promoter.

[00167] In some embodiments, the promoter is optimized for use with an AAV5, AAV6 or AAV8 vector.

[00168] In some embodiments, the promoter is tissue specific, and when operably linked with the AAV vector or the nucleotide that is a sequence that is complementary to at least one mutant allele on a target gene is active in the eye.

[00169] In some embodiments, the tissue specific promoter is active in the cornea or other anterior ocular tissues.

[00170] In some embodiments, the tissue specific promoter is active in the endothelium of the cornea.

[00171] In some embodiments, the target gene is preferentially expressed in the anterior portion of the eye. Preferably, the target gene is preferentially expressed in the cornea, and most preferably, preferentially expressed in the endothelium of the cornea.

[00172] In some embodiments, the delivery system, vector, nucleotide or gene editing system, or composition is preferentially expressed in the anterior portion of the eye after IC injection. Preferably, the delivery system, vector, nucleotide or gene editing system, or composition is preferentially expressed in the cornea, and most preferably, preferentially expressed in the endothelium of the cornea, after IC injection.

[00173] In some embodiments, the delivery system, vector, nucleotide or gene editing system, or composition is suitable for treating a disease or condition in the eye.

[00174] In some embodiments, the disease or condition in the eye is a disease or condition of the cornea.

[00175] In some embodiments, the disease or condition of the cornea is a superficial corneal dystrophy, anterior corneal dystrophy, corneal stromal dystrophy, or posterior cornea dystrophy.

[00176] In some embodiments, the disease or condition of the cornea is a posterior corneal dystrophy.

[00177] In some embodiments, the posterior corneal dystrophy is Fuchs endothelial corneal dystrophy (FECD; both early and late onset), posterior polymorphous dystrophy (PPCD; types 1, 2, and 3), congenital endothelial dystrophy (types 1 and 2), and X-linked endothelial corneal dystrophy.

[00178] In some embodiments, the corneal dystrophy is FECD.

EXAMPLES

Example 1. Methods of preparing and administering AAV vectors

AAV vectors

[00179] Wildtype AAV2, AAV5, AAV6, AAV8, and AAV9 vectors were produced by methods known in the art. Each AAV encoded for eGFP under the ubiquitous CAG promoter. Each AAV was supplied at 1×10^{13} vg/mL in a PBS + 0.001% pluronic acid formulation.

Intracameral (IC) injections

[00180] Adult male C57BL/6J mice (10-11 weeks old) were purchased from Jackson Laboratories. All animal procedures and handling were conducted according to the ARVO Statement for the use of Animals and the Regeneron Pharmaceuticals IACUC reviewed protocol. Mice were anesthetized with ketamine/xylazine mixture by intraperitoneal injection. The eyes were rinsed with sterile saline followed by a drop of tropicamide (to dilate the pupil) with a drop of proparacaine (to numb the cornea). Using a Drummond Scientific Nanoject II microinjection device fitted with a pulled glass needle (sandpaper beveled), AAV solution was filled into the needle and used to inject AAV solution into each anterior chamber. The glass needle was injected through the cornea, parallel to the iris, into the aqueous humor of the anterior chamber. A small amount of aqueous humor was allowed to leak out. Bubbles were pushed into cornea followed by 1.5 μ L of AAV solution, containing 1.5×10^{10} vg. The needle was held still after the injection for 30 sec and then pulled out in a quick smooth motion. Both OD (right eye) and OS (left eye) of each animal were injected. Control animals received injections of PBS+0.001% pluronic acid instead of AAV solution. Genteal ointment was applied to each eye to prevent corneal drying and abrasion while the mouse was placed on its ventral side (to prevent leakage and pooling) to recover from anesthesia.

Intravitreal injections

[00181] Adult male C57BL/6J mice (10-11 weeks old) were purchased from Jackson Laboratories. All animal procedures and handling were conducted according to the ARVO Statement for the use of Animals and the Regeneron Pharmaceuticals IACUC reviewed protocol. Mice were anesthetized with ketamine/xylazine mixture by intraperitoneal injection. The eyes were rinsed with sterile saline followed by a drop of tropicamide (to dilate the pupil) with a drop of proparacaine (to numb the cornea). Using a Drummond Scientific Nanoject II microinjection device fitted with a pulled glass needle (sandpaper beveled), AAV solution was filled into the needle and used to inject AAV solution into the vitreous humor of the vitreous chamber. The glass needle was injected through the sclera at the limbus of the eye into the vitreous chamber. 1.5 μ L of AAV solution, containing 1.5×10^9 vg, was injected into the vitreous chamber using the microinjection device. The needle was pulled out in a quick smooth motion. Both OD (right eye) and OS (left eye) of each animal were injected. Control animals received injections of PBS+0.001% pluronic acid instead of AAV solution. Genteal ointment was applied to each eye to prevent corneal drying and abrasion while the mouse was placed on its ventral side (to prevent leakage and pooling) to recover from anesthesia.

Example 2. Assessment of specificity of protein targeting to different tissues in the eye.

In Vivo imaging

[00182] In vivo imaging was performed at baseline prior to injections and at timepoints post injections using the Heidelberg Spectralis HRA+OCT (Heidelberg Engineering, Inc, Germany). Mice were anesthetized and a drop of tropicamide was applied to each eye to dilate the pupil, followed by a drop of proparacaine to numb the cornea. At each time point, infrared images and fluorescence images to detect AAV-eGFP fluorescence were taken of the posterior retinal fundus (+25 diopter small animal imaging lens) and the anterior cornea (anterior segment module). The FA modality on the Heidelberg Spectralis HRA+OCT was used to detect fluorescence of eGFP protein resulting from the AAV-eGFP injections.

Immunohistochemistry

[00183] Mice that received AAV-eGFP injections, such as AAV5-eGFP, AAV6-eGFP, and AAV8-eGFP, by intraocular injection were euthanized for enucleation of their eyes. Control

mice that received PBS+0.001% pluronic acid intraocular injections were euthanized for enucleation of their eyes. Each eye was enucleated and fixed in 4% PFA overnight at 4°C. The eyes were washed in PBS followed by incubation in 30% sucrose at 4°C for a minimum of 3 days. Eyes were then embedded in OCT embedding compound and a subset of the samples were sent for cross-sectioning by Histoserv Inc (Maryland). In order to amplify regions of AAV-eGFP localization, a primary antibody for eGFP was incubated on the slides containing cross-sectioned mouse eye tissues at 4°C overnight. The secondary antibody was conjugated to Alexa-Fluor 594 (red) to differentiate from the green endogenous eGFP unamplified signal. DAPI (blue) was added to the slides to label nuclei and aid in the identification of cellular types and regions.

[00184] The slides were imaged using the Keyence microscope (Keyence Corporation of America, Illinois, USA). Regions of green and/or red fluorescence were assessed for both anatomical ocular regions and cellular localization.

eGFP protein measurement

[00185] Four mice (whole eyes) for each of the AAV serotypes, such as AAV5-eGFP, AAV6-eGFP, AAV8-eGFP, delivered by intraocular injections were euthanized for enucleation of their eyes. Two mice that received PBS+0.001% pluronic acid were included as controls for each of the AAV serotypes tested and were euthanized for enucleation of their eyes. Each eye was kept separate and processed as an individual sample. The eyes were immersed in 1X cell extraction buffer PTR (provided in the ELISA kit) and were homogenized using a tissuelyzer with stainless steel beads. The samples were centrifuged and the protein containing lysate was collected. Total protein measurements were measured using the BCA kit (Pierce BCA Protein Assay kit, ThermoFisher). Samples were assayed in triplicates for eGFP protein expression using the GFP SimpleStep ELISA kit (Abcam). eGFP expression per eye was calculated as ng/μg of total protein isolated from the eye.

[00186] Transduction efficiency and tropism varied depending on the AAV serotype used. Using Heidelberg Spectralis in vivo imaging, regions of AAV transduction after IC administration were determined. AAV2, AAV6, AAV8, and AAV9 were found to target both the posterior and anterior segments of the eye after IC administration with AAV2, AAV6, and AAV9 showing the strongest eGFP expression in the anterior segment, whereas AAV5

targets only anterior ocular tissues. The data also indicate that that AAV5, AAV6, and AAV8 have a strong tropism for anterior regions after IC injections. Additionally, IC injections are also capable of delivering AAVs to the posterior tissues, as shown by the strong tropism of AAV2 and AAV9 to the posterior regions after IC injections.

Example 3. Correction of a gene mutation in the endothelial cells of the cornea

[00187] Corrections of target gene mutations such as mutations in *TCF4* or *COL8A2* in the endothelial cells of the cornea are done by administering a composition comprising a nucleic acid editing system comprising a CRISPR/Cas complex.

[00188] The CRISPR/Cas complex comprises a guide sequence that is complementary to a portion of the target gene containing the mutation and is directed to the target DNA sequence, and an endonuclease encoding for a Cas nuclease.

[00189] The CRISPR/Cas complex is guided to the target sequence, and the Cas nuclease cleaves the target sequence. A gene insertion mutation is corrected by cleaving the target sequence, and repairing the break in the DNA. A gene mutation that is a change in a nucleotide is corrected by cleaving the mutated sequence nucleotide sequence, and repairing the DNA with a repair template comprising the nucleotide sequence of the wild-type gene.

[00190] The CRISPR/Cas complex is preferably packaged in an AAV vector, such as AAV5, AAV6 or AAV8. AAV vectors are produced by methods known in the art. Each AAV encodes for a target sequence under the ubiquitous CAG promoter. Each AAV is supplied at 1e13g/mL in a PBS + 0.001% pluronic acid formulation.

[00191] The AAV vector packaged with the CRISPR/Cas complex is administered directly to the anterior chamber of the eye via intracameral injection. Mice carrying such mutations are anesthetized with ketamine/xylazine mixture by intraperitoneal injection. The eyes are rinsed with sterile saline followed by a drop of tropicamide (to dilate the pupil) with a drop of proparacaine (to numb the cornea). Using a Drummond Scientific Nanoject II microinjection device fitted with a pulled glass needle (sandpaper beveled), AAV solution is filled into the needle and used to inject AAV solution into each anterior chamber. The glass needle is injected through the cornea, parallel to the iris, into the aqueous humor of the anterior

chamber. A small amount of aqueous humor is allowed to leak out. Bubbles are pushed into cornea followed by 1.5 μ L of AAV solution, containing 1.5×10^9 vg. The needle is held still after the injection for 30 sec and then pulled out in a quick smooth motion. Both OD (right eye) and OS (left eye) of each animal are injected. Control animals receive injections of PBS+0.001% pluronic acid instead of AAV solution. Genteal ointment is applied to each eye to prevent corneal drying and abrasion while the mouse is placed on its ventral side (to prevent leakage and pooling) to recover from anesthesia.

[00192] Corrections of gene expression is confirmed by dissecting corneas (as well as isolating endothelial cells from said corneas) from the eyes of treated and control mice, and doing DNA and/or RNA nucleic acid sequencing.

Example 4 - Downregulation of gene expression in the endothelial cells of the cornea.

[00193] Gene expression is downregulated by administering a composition comprising at least one inhibitory nucleotide sequence that is complementary to at least one allele on a target gene, selected from an siRNA, an shRNA, an miRNA, an antisense RNA, or an antagomir RNA. The target gene is any cornea mutated gene such as *TCF4* or *COL8A2*. The inhibitory RNA is present in the composition by itself, or as part of a CRISPR/Cas complex.

[00194] The inhibitory RNA is packaged in an AAV vector similarly to Example 3. The inhibitory RNA is preferably packaged in an AAV vector, such as AAV5, AAV6 or AAV8. AAV vectors are produced by methods known in the art. Each AAV encodes for a target sequence under the ubiquitous CAG promoter. Each AAV is supplied at 1×10^{13} g/mL in a PBS + 0.001% pluronic acid formulation.

[00195] Similarly to Example 3, the AAV vector packaged with the inhibitory RNA is administered directly to the anterior chamber of the eye via intracameral injection. Mice are anesthetized with ketamine/xylazine mixture by intraperitoneal injection. The eyes are rinsed with sterile saline followed by a drop of tropicamide (to dilate the pupil) with a drop of proparacaine (to numb the cornea). Using a Drummond Scientific Nanoject II microinjection device fitted with a pulled glass needle (sandpaper beveled), AAV solution is filled into the needle and used to inject AAV solution into each anterior chamber. The glass needle is

injected through the cornea, parallel to the iris, into the aqueous humor of the anterior chamber. A small amount of aqueous humor is allowed to leak out. Bubbles are pushed into the cornea followed by 1.5 μ L of AAV solution, containing 1.5×10^{10} vg. The needle is held still after the injection for 30 sec and then pulled out in a quick smooth motion. Both OD (right eye) and OS (left eye) of each animal are injected. Control animals receive injections of PBS+0.001% pluronic acid instead of AAV solution. Genteal ointment is applied to each eye to prevent corneal drying and abrasion while the mouse is placed on its ventral side (to prevent leakage and pooling) to recover from anesthesia.

[00196] Downregulation of gene expression is confirmed by dissecting corneas from the eyes of treated and control mice, and measuring the amount of the protein encoded by the gene in the samples via Western blot. Successful downregulation of gene expression results in reduced levels of the encoded protein in corneal tissue from treated mice versus control mice.

[00197] The present invention has been described in detail, including the preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of the present disclosure, may make modifications and/or improvements on this invention that fall within the scope and spirit of the invention.

Sequence	Description	SEQ ID NO.
	sequence “N” may be any natural or non-natural nucleotide.	
AACAGCAUAGCAAGUUAAAAUAAGGCUAGUCCGUUAUCAA CUUGAAAAAGUGGCACCGAGUCGGUGCUUUUUUU	trRNA sequence	1088

Attorney Docket No.: 67000-1023 WO

Table 1. *TCF4* target sequences and corresponding guide sequences

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
1	TGGCAAGTGGAC ATTTTACTGG	Chr18:5585285- 5585307	-	5' of TNRs of TCF4	-871	1089	UUGGCAAGUG GACAUUUUAC
2	TGTCACACTGGCA AAGAAGTTGG	Chr18:5585294- 5585316	+	5' of TNRs of TCF4	-862	1090	UGUCCACUUG CCAAAGAAAGU
3	GGACCAACTT CTTTGGCAAGTGG	Chr18:5585297- 5585319	-	5' of TNRs of TCF4	-859	1091	GGACCAACUU CUUUGGCAAG
4	GAAATATGGA CCAACTTCTTTGG	Chr18:5585304- 5585326	-	5' of TNRs of TCF4	-852	1092	GAAAAAUGGA CCAAACUUUUU
5	CCATTTTTC CACTGCTCACAGG	Chr18:5585318- 5585340	+	5' of TNRs of TCF4	-838	1093	CCAUUUUUUCC CACUGGCUAC
6	CCTGTGAGCA GTGGGAAAATGG	Chr18:5585318- 5585340	-	5' of TNRs of TCF4	-838	1094	CCUGUGAGCA GUGGGAAAAA
7	TTTTTCCCAC TGCTCACAGGAGG	Chr18:5585321- 5585343	+	5' of TNRs of TCF4	-835	1095	UUUUUUCCAC UGCUCACAGG
8	TTTTCACCTCC TGTGAGCAGTGGG	Chr18:5585326- 5585348	-	5' of TNRs of TCF4	-830	1096	UUUCACCUCC UGUGAGCAGU
9	TTTTACCTC CTGTGAGCAGTGG	Chr18:5585327- 5585349	-	5' of TNRs of TCF4	-829	1097	UUUUCACCUCC CUGUGAGCAG
10	AGATCTTTCA GGAGCTCTGAAGG	Chr18:5585399- 5585421	-	5' of TNRs of TCF4	-757	1098	AGAUCUUUGA GGAGCUCUGA
11	AACAGTATCA AAGATCTTTGAGG	Chr18:5585410- 5585432	-	5' of TNRs of TCF4	-746	1099	AACAGUAUGA AAGAUCUUUG
12	AGCATAAACT CTAAGCTGTTTGG	Chr18:5585434- 5585456	-	5' of TNRs of TCF4	-722	1100	AGCAUAAACU CUAAGCUGUU

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
13	ACAGCTTAGA GTTTATGCTAAGG	Chr18:55585438- 55585460	+	5' of TNRs of TCF4	-718	1101	ACAGCUUAGA GUUUAUGCUA
14	CAGCTTAGAG TTTATGCTAAGGG	Chr18:55585439- 55585461	+	5' of TNRs of TCF4	-717	1102	CAGCUUAGAG UUUAUGCUAA
15	TCTTTTAGTT TTAAGTTGGATGG	Chr18:55585483- 55585505	-	5' of TNRs of TCF4	-673	1103	UCUUUUAGUU UUAAAGUUGGA
16	TTTCTCTTTT AGTTTAAAGTTGG	Chr18:55585487- 55585509	-	5' of TNRs of TCF4	-669	1104	UUUCUCUUUU AGUUUUUAAAGU
17	GTGATAATGG GGGCTGGGTGGG	Chr18:55585523- 55585545	-	5' of TNRs of TCF4	-633	1105	GUGAUAAUGG GGGCUGGGGU
18	AGTGATAATG GGGCTGGGTGGG	Chr18:55585524- 55585546	-	5' of TNRs of TCF4	-632	1106	AGUGAUAAUG GGGCUGGGG
19	CAGAGTGATA ATGGGGCTGGGG	Chr18:55585527- 55585549	-	5' of TNRs of TCF4	-629	1107	CAGAGUGAUA AUGGGGGCUG
20	ACAGAGTGAT AATGGGGCTGGG	Chr18:55585528- 55585550	-	5' of TNRs of TCF4	-628	1108	ACAGAGUGAU AAUGGGGGCU
21	AACAGAGTGA TAATGGGGCTGGG	Chr18:55585529- 55585551	-	5' of TNRs of TCF4	-627	1109	AACAGAGUGA UAAUGGGGGC
22	AAAGAACAGA GTGATAATGGGGG	Chr18:55585533- 55585555	-	5' of TNRs of TCF4	-623	1110	AAAGAACAGA GUGAUAAUGG
23	GAAAGAACAG AGTGATAATGGGG	Chr18:55585534- 55585556	-	5' of TNRs of TCF4	-622	1111	GAAAGAACAG AGUGAUAAUG
24	AGAAAGAAC GAGTGATAATGGG	Chr18:55585535- 55585557	-	5' of TNRs of TCF4	-621	1112	AGAAAGAAC GAGUGAUAAU
25	AAGAAAGAAC AGAGTGATAATGG	Chr18:55585536- 55585558	-	5' of TNRs of TCF4	-620	1113	AAGAAAGAAC AGAGUGAUAA
26	TCTGTTCTTT CTTTTCTCTCAGG	Chr18:55585546- 55585568	+	5' of TNRs of TCF4	-610	1114	UCUGUUCUUU CUUUUUCCUC

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
27	TTTTCCTCAG GTTTCATTAGATGG	Chr18:55585558- 55585580	+	5' of TNRs of TCF4	-598	1115	UUUCCUCAG GUUCAUUAGA
28	TGGCCATCT AATGAACCTGAGG	Chr18:55585562- 55585584	-	5' of TNRs of TCF4	-594	1116	UUGGCCAUCU AAUGAACCCUG
29	AATGTAGCAG TAGTACTGCTTGG	Chr18:55585581- 55585603	-	5' of TNRs of TCF4	-575	1117	AAUGUAGCAG UAGUACUGCU
30	AGCAGTACTA CTGCTACATTTGG	Chr18:55585584- 55585606	+	5' of TNRs of TCF4	-572	1118	AGCAGUACUA CUGCUACAUU
31	TGAATCTTGA TAACATTATGGGG	Chr18:55585619- 55585641	-	5' of TNRs of TCF4	-537	1119	UGAAUCUUGA UACAUAUUG
32	CTGAATCTTG ATAACATTATGGG	Chr18:55585620- 55585642	-	5' of TNRs of TCF4	-536	1120	CUGAAUCUUG AUAAACAUAU
33	CCATAATGTT ATCAAGATTACAGG	Chr18:55585621- 55585643	+	5' of TNRs of TCF4	-535	1121	CCAUAUUGUU AUCAAGAUAUC
34	CCTGAATCTT GATAACATTATGG	Chr18:55585621- 55585643	-	5' of TNRs of TCF4	-535	1122	CCUGAAUCUU GAUAAACAUA
35	AATGTTATCA AGATTCAGGTTGG	Chr18:55585625- 55585647	+	5' of TNRs of TCF4	-531	1123	AAUGUUAUCA AGAUUCAGGU
36	GTTATCAAGA TTCAGGTTGGAGG	Chr18:55585628- 55585650	+	5' of TNRs of TCF4	-528	1124	GUUAUCAAGA UUCAGGUUGG
37	TGTTTTTCTA GAGAGGCTGCTGG	Chr18:55585651- 55585673	-	5' of TNRs of TCF4	-505	1125	UGUUUUUUCUA GAGAGGCUGC
38	AAACTAGTGT TTTTCTAGAGAGG	Chr18:55585658- 55585680	-	5' of TNRs of TCF4	-498	1126	AAACUAGUGU UUUUCUAGAG
39	GAAAAACACT AGTTTACCAAAGG	Chr18:55585666- 55585688	+	5' of TNRs of TCF4	-490	1127	GAAAAACACU AGUUUCACCA
40	AACAACTTTT TTCTTCTCCTTGG	Chr18:55585683- 55585705	-	5' of TNRs of TCF4	-473	1128	AACAACUUUU UUCUUCUCCU

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
41	TTGTTTATA TTGAAAACCTTGG	Chr18:55585706-55585728	+	5' of TNRs of TCF4	-450	1129	UUGUUUUUAUA UUGAAAACCUU
42	GAAAACCTTG GCCATAAACGTGG	Chr18:55585718-55585740	+	5' of TNRs of TCF4	-438	1130	GAAAACCUUG GCCAUAAACG
43	CATTGCCACG TTTATGGCCAAAGG	Chr18:55585723-55585745	-	5' of TNRs of TCF4	-433	1131	CAUUGCCACG UUUAUGGCCA
44	AATGGACATT GCCACGTTTATGG	Chr18:55585729-55585751	-	5' of TNRs of TCF4	-427	1132	AAUGGACAUU GCCACGUUUA
45	TGTCCATTTC CATCTCGTATAGG	Chr18:55585744-55585766	+	5' of TNRs of TCF4	-412	1133	UGUCCAUUUC CAUCUCGUAU
46	AATCCTATAC GAGATGGAATGG	Chr18:55585747-55585769	-	5' of TNRs of TCF4	-409	1134	AAUCCUUAUAC GAGAUUGGAAA
47	CAGGCAAAATC CTATACGAGATGG	Chr18:55585753-55585775	-	5' of TNRs of TCF4	-403	1135	CAGGCAAAUC CUAUACGAGA
48	TATTTGGGTT CACATATGACAGG	Chr18:55585772-55585794	-	5' of TNRs of TCF4	-384	1136	UAUUUGGGUU CACAUUAUGAC
49	TGGCACTTTT ATTTTATTTGGG	Chr18:55585787-55585809	-	5' of TNRs of TCF4	-369	1137	UGGCACUUUU AUUUUUUAUUU
50	GTGGCACTTT TATTTTATTTGG	Chr18:55585788-55585810	-	5' of TNRs of TCF4	-368	1138	GUGGCACUUU UAUUUUUAUU
51	AAATGAGAAT TTAGTGCAGGTGG	Chr18:55585807-55585829	-	5' of TNRs of TCF4	-349	1139	AAAUGAGAAU UUAGUGCAGG
52	ACGAAATGAG AATTAGTGCAGG	Chr18:55585810-55585832	-	5' of TNRs of TCF4	-346	1140	ACGAAAUGAG AAUUUAUGUC
53	ATTCTCATTT CGTCTCTAACAGG	Chr18:55585820-55585842	+	5' of TNRs of TCF4	-336	1141	AUUCUCAUUU CGUCUCUAAAC
54	AAATAAATGC TGGAGAGAGAGGG	Chr18:55585898-55585920	-	5' of TNRs of TCF4	-258	1142	AAAUAAAUGC UGGAGAGAGA

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
55	GAAATAAATG CTGGAGAGAGAGG	Chr18:55585899- 55585921	-	5' of TNRs of TCF4	-257	1143	GAAAUAAAUG CUGGAGAGAG
56	ATTAGGGTCG AAATAAATGCTGG	Chr18:55585908- 55585930	-	5' of TNRs of TCF4	-248	1144	AUUAGGGGUCG AAAUAAAUGC
57	GCATTTATTT CGACCCCTAATTGG	Chr18:55585911- 55585933	+	5' of TNRs of TCF4	-245	1145	GCAUUUAUUU CGACCCUAAU
58	AAGAAAGAGGG AAACCAATTAGGG	Chr18:55585924- 55585946	-	5' of TNRs of TCF4	-232	1146	AAGAAAGAGGG AAACCAAUUA
59	GAAGAAAGAGG GAAACCAATTAGG	Chr18:55585925- 55585947	-	5' of TNRs of TCF4	-231	1147	GAAGAAAGAGG GAAACCAAUU
60	ACTAGATACG TCGAAGAAGAGGG	Chr18:55585937- 55585959	-	5' of TNRs of TCF4	-219	1148	ACUAGAUACG UCGAAAGAAGA
61	CAC TAGATAC GTCGAAGAAGAGG	Chr18:55585938- 55585960	-	5' of TNRs of TCF4	-218	1149	CACUAGAUAUAC GUCGAAGAAG
62	CTCTTCTTCG ACGTATCTAGTGG	Chr18:55585939- 55585961	+	5' of TNRs of TCF4	-217	1150	CUCUUCUUCG ACGUAUCUAG
63	TGCAGGCTCT GACTCAGGGAAGG	Chr18:55585972- 55585994	-	5' of TNRs of TCF4	-184	1151	UGCAGGCUCU GACUCAGGGA
64	TTTTTGCAGG CTCTGACTCAGGG	Chr18:55585976- 55585998	-	5' of TNRs of TCF4	-180	1152	UUUUUGCAGG CUCUGACUCA
65	CTTTTTCGAG GCTCTGACTCAGG	Chr18:55585977- 55585999	-	5' of TNRs of TCF4	-179	1153	CUUUUUGCAG GCUCUGACUC
66	TCAGAGCCCTG CAAAAAGCAAAGG	Chr18:55585983- 55586005	+	5' of TNRs of TCF4	-173	1154	UCAGAGCCUG CAAAAAGCAA
67	TTGCTTCCCTT TGCTTTTTCGAGG	Chr18:55585989- 55586011	-	5' of TNRs of TCF4	-167	1155	UUCGUUCCUU UGC UUUUUGC
68	GCAAAAAGCA AAGGAACGAATGG	Chr18:55585992- 55586014	+	5' of TNRs of TCF4	-164	1156	GCAAAAAGCA AAGGAACGAA

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
69	AGAAAAGTGCA ACAAGCAGAAAGG	Chr18:55586015-55586037	+	5' of TNRs of TCF4	-141	1157	AGAAAAGUGCA ACAAGCAGAA
70	GAAAGTGCAA CAAGCAGAAAGG	Chr18:55586016-55586038	+	5' of TNRs of TCF4	-140	1158	GAAAGUGCAA CAAGCAGAAA
71	AAAGTGCAAC AAGCAGAAAGGG	Chr18:55586017-55586039	+	5' of TNRs of TCF4	-139	1159	AAAGUGCAAC AAGCAGAAAG
72	AAGTGCAACA AGCAGAAAGGGG	Chr18:55586018-55586040	+	5' of TNRs of TCF4	-138	1160	AAGUGCAACA AGCAGAAAGG
73	GGCTGCAAG CTGCCCTGCTAGG	Chr18:55586039-55586061	+	5' of TNRs of TCF4	-117	1161	GGCUGCAAG CUGCCUGCCU
74	GCTGCAAGC TGCCCTGCTAGG	Chr18:55586040-55586062	+	5' of TNRs of TCF4	-116	1162	GCUGCAAGC UGCCUGCCUA
75	CACGAAACGT AGCCCTAGGCAGG	Chr18:55586052-55586074	-	5' of TNRs of TCF4	-104	1163	CAGCAAAACGU AGCCCUAGGC
76	CTGCCCTAGG CTACGTTTCCTGG	Chr18:55586053-55586075	+	5' of TNRs of TCF4	-103	1164	CUGCCUAGGG CUACGUUUCC
77	TTGCCAGGAA ACGTAGCCCTAGG	Chr18:55586056-55586078	-	5' of TNRs of TCF4	-100	1165	UUGCCAGGAA ACGUAGCCCU
78	TGGCTTTGG AAGTTTGGCCAGG	Chr18:55586071-55586093	-	5' of TNRs of TCF4	-85	1166	UGGCUUUUGG AAGUUUUUGCC
79	TCTTTTGGAG AAATGCCCTTTCGG	Chr18:55586084-55586106	-	5' of TNRs of TCF4	-72	1167	UCUUUUUGGAG AAAUUGCCUUU
80	AAAGCCATTT CTCCAAAGAGAGG	Chr18:55586087-55586109	+	5' of TNRs of TCF4	-69	1168	AAAGCCAUUU CUCCAAAAGA
81	TAGACCTTCT TTTGGACAAAATGG	Chr18:55586091-55586113	-	5' of TNRs of TCF4	-65	1169	UAGACCUUCU UUUGGAGAAA
82	TCCAAAAGAA GCTCTAGAGAGG	Chr18:55586098-55586120	+	5' of TNRs of TCF4	-58	1170	UCCAAAAGAA GGUCUACAAG

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
83	TCCCTCTTCTA GACCTTCTTTTGG	Chr18:55586099- 55586121	-	5' of TNRs of TCF4	-57	1171	UCCUCUUCUA GACCUUCUUU
84	AAAAGAAGGT CTAGAAGAGGAGG	Chr18:55586101- 55586123	+	5' of TNRs of TCF4	-55	1172	AAAAGAAGGU CUAGAAGAGG
85	AGAAAGGTCTA GAAGAGGAGGAGG	Chr18:55586104- 55586126	+	5' of TNRs of TCF4	-52	1173	AGAAAGGUCUA GAAGAGGAGG
86	AGGTCTAGAA GAGGAGGAGGAGG	Chr18:55586107- 55586129	+	5' of TNRs of TCF4	-49	1174	AGGUCUAGAA GAGGAGGAGG
87	TCTAGAAGAG GAGGAGGAGGAGG	Chr18:55586110- 55586132	+	5' of TNRs of TCF4	-46	1175	UCUAGAAGAG GAGGAGGAGG
88	AGAGGAGGAG GAGGAGGAGAAAGG	Chr18:55586116- 55586138	+	5' of TNRs of TCF4	-40	1176	AGAGGAGGAG GAGGAGGAGA
89	GGAGGAGGAG GAGGAGAAAGGAGG	Chr18:55586119- 55586141	+	5' of TNRs of TCF4	-37	1177	GGAGGAGGAG GAGGAGAAAGG
90	GGAGGAGGAG GAGAAGGAGGAGG	Chr18:55586122- 55586144	+	5' of TNRs of TCF4	-34	1178	GGAGGAGGAG GAGAAAGGAGG
91	GGAGGAGGAG AAGGAGGAGGAGG	Chr18:55586125- 55586147	+	5' of TNRs of TCF4	-31	1179	GGAGGAGGAG AAGGAGGAGG
92	GGAGGAGAAG GAGGAGGAGGAGG	Chr18:55586128- 55586150	+	5' of TNRs of TCF4	-28	1180	GGAGGAGAAG GAGGAGGAGG
93	GGAGAAAGGAG GAGGAGGAGGAGG	Chr18:55586131- 55586153	+	5' of TNRs of TCF4	-25	1181	GGAGAAAGGAG GAGGAGGAGG
94	CAGCATGAAA GAGCCCCACTTGG	Chr18:55586225- 55586247	+	3' of TNRs of TCF4	69	1182	CAGCAUGAAA GAGCCCCACU
95	ATGAAAGAGC CCCACTTGAAAGG	Chr18:55586229- 55586251	+	3' of TNRs of TCF4	73	1183	AUGAAAAGAGC CCCACUUGGA
96	AAAGAGCCCC ACTTGGAAAGCGG	Chr18:55586232- 55586254	+	3' of TNRs of TCF4	76	1184	AAAGAGCCCC ACUUGGAAGG

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
97	GCCCCACTTG GAAGGCGGTTTG	Chr18:55586237-55586259	+	3' of TNRs of TCF4	81	1185	GCCCCACUUG GAAGGCGGUU
98	TCCAAACCGC CTTCCAAGTG GGG	Chr18:55586238-55586260	-	3' of TNRs of TCF4	82	1186	UCCAAACCGC CUUCCAAGUG
99	ATCCAAACCG CCTTCCAAGTGG	Chr18:55586239-55586261	-	3' of TNRs of TCF4	83	1187	AUCCAAACCG CCUCCAAGU
100	AATCCAAACC GCCCTCCAAGTGG	Chr18:55586240-55586262	-	3' of TNRs of TCF4	84	1188	AAUCCAAACC GCCUCCAAG
101	GATTTTATTT GTGTGTTTGTGG	Chr18:55586259-55586281	+	3' of TNRs of TCF4	103	1189	GAUUUUAUUU GUGUGUUUUG
102	CATCTTACAC CAAACTCATCTGG	Chr18:55586308-55586330	+	3' of TNRs of TCF4	152	1190	CAUCUUACAC CAAAACUCAUC
103	TTTTTAATGC CAGATGAGTTTG	Chr18:55586317-55586339	-	3' of TNRs of TCF4	161	1191	UUUUUAAUGC CAGAUGAGUU
104	ATTCATTCTC CTGACATGTCTGG	Chr18:55586343-55586365	+	3' of TNRs of TCF4	187	1192	AUUCAUUCUC CUGACAUGUC
105	TTCAATCTCC TGACATGTCTGGG	Chr18:55586344-55586366	+	3' of TNRs of TCF4	188	1193	UUCAUUCUCC UGACAUGUCU
106	CTCCTGACAT GTCTGGGACTTGG	Chr18:55586350-55586372	+	3' of TNRs of TCF4	194	1194	CUCCUGACAU GUCUGGGACU
107	AACCAAGTCC CAGACATGTCAGG	Chr18:55586352-55586374	-	3' of TNRs of TCF4	196	1195	AACCAAGUCC CAGACAUGUC
108	ACATGTCTGG GACTTGGTTTAGG	Chr18:55586356-55586378	+	3' of TNRs of TCF4	200	1196	ACAUGUCUGG GACUUGGUUU
109	CTGGGACTTG GTTTAGGAAAAGG	Chr18:55586362-55586384	+	3' of TNRs of TCF4	206	1197	CUGGGACUUG GUUAGGAAA

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
110	GGTTTAGGAA AAGGAAGCAAAAGG	Chr18:55586371- 55586393	+	3' of TNRs of TCF4	215	1198	GGUUUAGGAA AAGGAAGCAA
111	GTTTAGGAAA AGGAAGCAAAAGG	Chr18:55586372- 55586394	+	3' of TNRs of TCF4	216	1199	GUUUAGGAAA AGGAAGCAAA
112	AGGAAAAGGA AGCAAGGGATGG	Chr18:55586376- 55586398	+	3' of TNRs of TCF4	220	1200	AGGAAAAGGA AGCAAAAGGA
113	AGGAAGCAAA GGGATGGAGAAAGG	Chr18:55586382- 55586404	+	3' of TNRs of TCF4	226	1201	AGGAAGCAAA GGGAUUGGAGA
114	TGGAGTTTAA CGGCTGTACTTGG	Chr18:55586406- 55586428	-	3' of TNRs of TCF4	250	1202	UGGAGUUUUA CGGCUGUACU
115	GACACACTTG TGGAGTTTACGG	Chr18:55586416- 55586438	-	3' of TNRs of TCF4	260	1203	GACACACUUG UGGAGUUUUA
116	AGCGGAACCT GACACACTTGTGG	Chr18:55586426- 55586448	-	3' of TNRs of TCF4	270	1204	AGCGGAACUU GACACACUUG
117	GTCGTAGGAT CAGCACAAAGCGG	Chr18:55586444- 55586466	-	3' of TNRs of TCF4	288	1205	GUCGUAGGAU CAGCACAAAG
118	TTGGTAAATT TCGTAGTCGTAGG	Chr18:55586459- 55586481	-	3' of TNRs of TCF4	303	1206	UUGGUAAAUU UCGUAGUCGU
119	ATTACCAAA ACAGTCCAAAAGG	Chr18:55586473- 55586495	+	3' of TNRs of TCF4	317	1207	AUUUACCAAA ACAGUCCAAA
120	TAGAACCTTT TGGACTGTTTGG	Chr18:55586478- 55586500	-	3' of TNRs of TCF4	322	1208	UAGAAACCUUU UGGACUGUUU
121	ATACATTCTT TAGAACCTTTTGG	Chr18:55586488- 55586510	-	3' of TNRs of TCF4	332	1209	AUACAUCUU UAGAAACCUUU
122	TAGGATTCTT AAAACCTAGTATGG	Chr18:55586522- 55586544	-	3' of TNRs of TCF4	366	1210	UAGGAUUCUU AAAACUAGUA
123	ATACTAGTTT TAAGAAATCCTAGG	Chr18:55586524- 55586546	+	3' of TNRs of TCF4	368	1211	AUACUAGUUU UAGAAAUCCU

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
124	TCCTAGGAAA AGATGTAAGTAGG	Chr18:55586540-55586562	+	3' of TNRs of TCF4	384	1212	UCCUAGGAAA AGAUGUAACU
125	TCCTAGTTAC ATCTTTTCTTAGG	Chr18:55586541-55586563	-	3' of TNRs of TCF4	385	1213	UCCUAGUUAC AUCUUUUUCCU
126	TAGGAAAAAGA TGTAAGTAGGAGG	Chr18:55586543-55586565	+	3' of TNRs of TCF4	387	1214	UAGGAAAAAGA UGUAAACUAGG
127	TAACTAGGAG GTAAGATGTAAGG	Chr18:55586555-55586577	+	3' of TNRs of TCF4	399	1215	UAAACUAGGAG GUAAGAUGUA
128	GGAGGTAAGA TGTAAGGAACAGG	Chr18:55586561-55586583	+	3' of TNRs of TCF4	405	1216	GGAGGUAAGA UGUAAAGGAAC
129	TAAATGATGCT TTGGATTGGTAGG	Chr18:55586585-55586607	-	3' of TNRs of TCF4	429	1217	UAAUGAUGCU UUGGAUUUGGU
130	AAGCTAATGA TGCTTTGGATTGG	Chr18:55586589-55586611	-	3' of TNRs of TCF4	433	1218	AAGCUAAUGA UGC UUUGGAU
131	GTTTAAAGCT AATGATGCTTTGG	Chr18:55586594-55586616	-	3' of TNRs of TCF4	438	1219	GUUUUAAAGCU AAUGAUGCUU
132	TAAAACTTTA AAGAGACAACCTGG	Chr18:55586611-55586633	+	3' of TNRs of TCF4	455	1220	UAAAAACUUUA AAGAGACAAC
133	AAAACCTTTAA AGAGACAACCTGGG	Chr18:55586612-55586634	+	3' of TNRs of TCF4	456	1221	AAAACUUUAAA AGAGACAACU
134	GGAAATGGAA AATAGAAAAATAGG	Chr18:55586638-55586660	-	3' of TNRs of TCF4	482	1222	GGAAAAUGGAA AAUAGAAAAU
135	TTATTTATTG TTTTTGGAAATGG	Chr18:55586653-55586675	-	3' of TNRs of TCF4	497	1223	UUAUUUAUUG UUUUUGGAAA
136	TTCGTTTTAT TTATTTGTTTTTGG	Chr18:55586659-55586681	-	3' of TNRs of TCF4	503	1224	UUCGUUUUAU UUAUUUGUUU
137	GTAATCTCAG TGTTTCAGACATGG	Chr18:55586702-55586724	+	3' of TNRs of TCF4	546	1225	GUAGUCUCAG UGUUCAGACA

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
138	TTCAGACATG GCCAAGTTTAGG	Chr18:55586714-55586736	+	3' of TNRs of TCF4	558	1226	UUCAGACAUG GCCAAGUUUU
139	TCAGACATGG CCAAGTTTAGGG	Chr18:55586715-55586737	+	3' of TNRs of TCF4	559	1227	UCAGACAUGG CCAAGUUUUA
140	CAGACATGGC CAAGTTTAGGGG	Chr18:55586716-55586738	+	3' of TNRs of TCF4	560	1228	CAGACAUGGC CAAGUUUUAG
141	ACATGGCCAA GTTTAGGGGTGG	Chr18:55586719-55586741	+	3' of TNRs of TCF4	563	1229	ACAUGGCCAA GUUUUAGGGG
142	ACTAAACCAC CCCTAAAACTTGG	Chr18:55586725-55586747	-	3' of TNRs of TCF4	569	1230	ACUAAACCAC CCCUAAAACU
143	TTTAGGGGTG GTTTAGTTTAGG	Chr18:55586731-55586753	+	3' of TNRs of TCF4	575	1231	UUUAGGGGUG GUUUAGUUUU
144	TTAGGGGTGG TTTAGTTTAGGG	Chr18:55586732-55586754	+	3' of TNRs of TCF4	576	1232	UUAGGGGUGG UUUAGUUUUA
145	TAGGGGTGGT TTAGTTTAGGGG	Chr18:55586733-55586755	+	3' of TNRs of TCF4	577	1233	UAGGGGUGGU UUAGUUUUAG
146	TGTCATTTT TGCTTCCACTGG	Chr18:55586756-55586778	+	3' of TNRs of TCF4	600	1234	UGUCUAUUUU UGC UUUCCAC
147	GTCTATTTT GCTTCCACTGGG	Chr18:55586757-55586779	+	3' of TNRs of TCF4	601	1235	GUCUAUUUUU GCUUUCCACU
148	TCTATTTTGG CTTTCACACTGGG	Chr18:55586758-55586780	+	3' of TNRs of TCF4	602	1236	UCUAUUUUUG CUUUCCACUG
149	ATAATGGAAT CTCACCCCAGTGG	Chr18:55586772-55586794	-	3' of TNRs of TCF4	616	1237	AUAAUGGAAU CUCACCCCAG
150	TGGGGTGAGA TTCATTATTTGG	Chr18:55586776-55586798	+	3' of TNRs of TCF4	620	1238	UGGGGUGAGA UUCCAUUAAU
151	GGGGTGAGAT TCCATTATTTGGG	Chr18:55586777-55586799	+	3' of TNRs of TCF4	621	1239	GGGGUGAGAU UCCAUAUUUU

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
152	GGGTGAGATT CCATTATTGGGG	Chr18:55586778- 55586800	+	3' of TNRs of TCF4	622	1240	GGGUGAGAUU CCAUUAUUUG
153	CCATTATTG GGTAATCAGTGG	Chr18:55586788- 55586810	+	3' of TNRs of TCF4	632	1241	CCAUUAUUUG GGGUAUCAG
154	CCACTGATTA CCCCAAATAATGG	Chr18:55586788- 55586810	-	3' of TNRs of TCF4	632	1242	CCACUGAUUA CCCCAAAUAA
155	CATTATTGG GGTAATCAGTGG	Chr18:55586789- 55586811	+	3' of TNRs of TCF4	633	1243	CAUUAUUUGG GGUAAUCAGU
156	ATTTGGGGTA ATCAGTGGGTAGG	Chr18:55586793- 55586815	+	3' of TNRs of TCF4	637	1244	AUUUGGGGUA AUCAGUGGGU
157	TTTGGGGTAA TCAGTGGGTAGG	Chr18:55586794- 55586816	+	3' of TNRs of TCF4	638	1245	UUUGGGGUAA UCAGUGGGUA
158	ATCAGTGGGT AGGGAATTGAAGG	Chr18:55586803- 55586825	+	3' of TNRs of TCF4	647	1246	AUCAGUGGGU AGGGAUUUGA
159	TTTTTTTTGA GTTTATTACTGG	Chr18:55586826- 55586848	-	3' of TNRs of TCF4	670	1247	UUUUUUUUGA GUUUUAUUAC
160	TGTGGTGTGA TGGAAAGATTCAGG	Chr18:55586856- 55586878	-	3' of TNRs of TCF4	700	1248	UGUGGUGUGA UGGAAAGAUUC
161	ACTATAATTT TGTGGTGTGATGG	Chr18:55586866- 55586888	-	3' of TNRs of TCF4	710	1249	ACUUAUAAUUU UGUGGUGUGA
162	AGTTTTTAAAC TATAATTTTGTGG	Chr18:55586874- 55586896	-	3' of TNRs of TCF4	718	1250	AGUUUUUUAAC UAUAAUUUUUG
163	AAAGACCTTC ATATTTACCAAGG	Chr18:55586903- 55586925	+	3' of TNRs of TCF4	747	1251	AAAGACCUUC AUAUUUACCA
164	TGAATCCTTG GTAAATATGAAGG	Chr18:55586908- 55586930	-	3' of TNRs of TCF4	752	1252	UGAAUCCUUG GUAAAAUAUGA
165	TTTTTAAATTG GCTGAATCCTTGG	Chr18:55586920- 55586942	-	3' of TNRs of TCF4	764	1253	UUUUUAAUUUG GCUGAAUCCU

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
166	GGACAGTAAT AATTTTAAATTGG	Chr18:55586932- 55586954	-	3' of TNRs of TCF4	776	1254	GGACAGUAAU AAUUUUUAAU
167	ACTGTCCTTT AGATTCCTACTGG	Chr18:55586948- 55586970	+	3' of TNRs of TCF4	792	1255	ACUGUCCUUU AGAUUCCUAC
168	AGAAACCAGT AGGAATCTAAAGG	Chr18:55586953- 55586975	-	3' of TNRs of TCF4	797	1256	AGAAACCAGU AGGAUUCUAA
169	CAC TTCAGT AGAAACCAGTAGG	Chr18:55586963- 55586985	-	3' of TNRs of TCF4	807	1257	CACUUCAGCU AGAAACCAGU
170	TGGTTCTAG CTGAAGTGTGG	Chr18:55586968- 55586990	+	3' of TNRs of TCF4	812	1258	UGGUUUCUAG CUGAAGUGUU
171	GGTTCTAGC TGAAAGTGTGG	Chr18:55586969- 55586991	+	3' of TNRs of TCF4	813	1259	GGUUUCUAGC UGAAGUGUUU
172	AGTGCGGTAA GAAAGAACGGTGG	Chr18:55587028- 55587050	-	3' of TNRs of TCF4	872	1260	AGUGCGGUAA GAAAGAACGG
173	TTCAGTGCGG TAAAGAAAGAACGG	Chr18:55587031- 55587053	-	3' of TNRs of TCF4	875	1261	UUCAGUGCGG UAGAGAAAGAA
174	TGATTTACTG GATTCAGTGCGG	Chr18:55587044- 55587066	-	3' of TNRs of TCF4	888	1262	UGAUUUUACUG GAUUUUCAGUG
175	CAAAGAGCTG AGTGATTTACTGG	Chr18:55587056- 55587078	-	3' of TNRs of TCF4	900	1263	CAAAGAGCUG AGUGAUUUAC
176	CAGCTCTTTG TCCGTCCTTAAGG	Chr18:55587069- 55587091	+	3' of TNRs of TCF4	913	1264	CAGCUCUUUG UCCGUGCCCUA
177	GCGAATGGCT GCCTTAGGACGG	Chr18:55587080- 55587102	-	3' of TNRs of TCF4	924	1265	GCGAAUGGCU GCCUUAGGGA
178	AACAGCGAAT GGCTGCCTTAGGG	Chr18:55587084- 55587106	-	3' of TNRs of TCF4	928	1266	AACAGCGAAU GGCUGCCCUA
179	CAACAGCGAA TGGCTGCCTTAGG	Chr18:55587085- 55587107	-	3' of TNRs of TCF4	929	1267	CAACAGCGAA UGGCUGCCCUU

SEQ ID NO	Target sequence (including PAM)	Chromosomal location	Strand	Orientation	Distance to start of TNR	SEQ ID NO	Guide sequence
180	CTAAGGCAGC CATTCGCTGTTGG	Chr18:55587086- 55587108	+	3' of TNRs of TCF4	930	1268	CUAAGGCAGC CAUUCGCUGU
181	AATGCATCAC CAACAGCGAATGG	Chr18:55587095- 55587117	-	3' of TNRs of TCF4	939	1269	AAUGCAUCAC CAACAGCGAA
182	ATCACACAAA CCTAGAAACATGG	Chr18:55587126- 55587148	+	3' of TNRs of TCF4	970	1270	AUCACACAAA CCUAGAAACA
183	GCGGTTATTT CCATGTTTCTAGG	Chr18:55587136- 55587158	-	3' of TNRs of TCF4	980	1271	GCGGUUAUUU CCAUGUUUCU
184	GGGACTGGAT TTTCTGATTGCGG	Chr18:55587155- 55587177	-	3' of TNRs of TCF4	999	1272	GGGACUGGAU UUUCUGAUUG
185	GAAAATCCAG TCCCAATCCTTGG	Chr18:55587164- 55587186	+	3' of TNRs of TCF4	1008	1273	GAAAAUCCAG UCCCAAUCCU
186	TTTTCTCCAA GGATTGGGACTGG	Chr18:55587170- 55587192	-	3' of TNRs of TCF4	1014	1274	UUUUCUCCAA GGAUUGGGAC
187	TTGTGTTTTC TCCAAGGATTGGG	Chr18:55587175- 55587197	-	3' of TNRs of TCF4	1019	1275	UUGUGUUUUC UCCAAAGGAUU
188	ATTGTGTTTT CTCCAAGGATTGG	Chr18:55587176- 55587198	-	3' of TNRs of TCF4	1020	1276	AUUGUGUUUU CUCCAAAGGAU
189	ATCCTTGGAG AAACACACAATCGG	Chr18:55587179- 55587201	+	3' of TNRs of TCF4	1023	1277	AUCCUUGGAG AAAACACAAU
190	ATCCGATTGT GTTTCTCCAAGG	Chr18:55587181- 55587203	-	3' of TNRs of TCF4	1025	1278	AUCCGAUUGU GUUUUCUCCA

Table 2. Combinations of *TCF4* guide sequences

SEQ ID NOs (5' Target Sequence)	SEQ ID NOs (3' Target Sequence)
83	109
85	109
86	112
85	125
86	109
85	107
83	125
86	125
86	107
64	106
85	114
86	114
83	114
53	114
83	112
74	114
85	108
83	107
85	115
58	109
86	108
83	96
74	109
77	115
53	96
83	108
74	125
85	94
86	96
53	107
83	94
71	115
77	96
58	112
77	109
85	95
53	94
77	95
86	115
85	96

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SEQ ID NOs (5' Target Sequence)	SEQ ID NOs (3' Target Sequence)
58	94
58	115
71	96
58	107
83	95
58	96
77	94
56	94
77	108
77	112
86	94
77	107
86	95
56	96
54	94
71	94
77	114
71	114
56	95
58	95
53	112
71	109
74	112
54	96
58	114
74	108
53	108
74	107
74	94
71	107
71	95
71	112
74	96
74	95
74	115
54	95
53	95
77	125
54	112
56	114
73	101
54	109
54	114

SEQ ID NOs (5' Target Sequence)	SEQ ID NOs (3' Target Sequence)
54	107
54	108
54	115
56	109
56	107
56	108
56	112
56	115
56	125
53	125

Table 3. Target sequences for wild-type *COL8A2* gene

SEQ ID No	Chromosomal location	Strand	Target sequence
191	Chr1:36097532-36097554	+	GGGGAGGAGGCCAGGGCAGCAGG
192	Chr1:36097545-36097567	+	GGGCAGCAGGACCCCCCCCCGCGG
193	Chr1:36097546-36097568	+	GGCAGCAGGACCCCCCCCCGCGGG
194	Chr1:36097554-36097576	+	GACCCCCCCCCGCGGGTTATGTGG
195	Chr1:36097555-36097577	+	ACCCCCCCCCGCGGGTTATGTGGG
196	Chr1:36097556-36097578	+	CCCCCCCCCGCGGGTTATGTGGGG
197	Chr1:36097556-36097578	-	CCCCACATAACCCGCGGGGGGGG
198	Chr1:36097557-36097579	-	GCCCCACATAACCCGCGGGGGGGG
199	Chr1:36097558-36097580	-	TGCCCCACATAACCCGCGGGGGG
200	Chr1:36097559-36097581	-	CTGCCCCACATAACCCGCGGGGGG
201	Chr1:36097560-36097582	-	TCTGCCCCACATAACCCGCGGGG
202	Chr1:36097561-36097583	-	CTCTGCCCCACATAACCCGCGGG
203	Chr1:36097562-36097584	-	GCTCTGCCCCACATAACCCGCGG
204	Chr1:36097578-36097600	+	GCAGAGCAAGAATCCTGAAAAGG
205	Chr1:36097581-36097603	+	GAGCAAGAATCCTGAAAAGGAGG
206	Chr1:36097586-36097608	+	AGAATCCTGAAAAGGAGGAGTGG
207	Chr1:36097591-36097613	-	TACATCCACTCCTCCTTTTCAGG
208	Chr1:36097599-36097621	+	GGAGGAGTGGATGTACTCCGTGG
209	Chr1:36097607-36097629	+	GGATGTACTCCGTGGAGTAGAGG
210	Chr1:36097614-36097636	+	CTCCGTGGAGTAGAGGCCGTGG
211	Chr1:36097616-36097638	-	GGCCAACGGCCTCTACTCCACGG
212	Chr1:36097619-36097641	+	TGGAGTAGAGGCCGTTGGCCTGG

SEQ ID No	Chromosomal location	Strand	Target sequence
213	Chr1:36097627-36097649	+	AGGCCGTTGGCCTGGTCCGACGG
214	Chr1:36097630-36097652	-	ATGCCGTCGGACCAGGCCAACGG
215	Chr1:36097637-36097659	-	GGTGCAGATGCCGTCGGACCAGG
216	Chr1:36097643-36097665	-	GGTCTGGGTGCAGATGCCGTCGG
217	Chr1:36097646-36097668	+	ACGGCATCTGCACCCAGACCTGG
218	Chr1:36097653-36097675	+	CTGCACCCAGACCTGGTCGTTGG
219	Chr1:36097654-36097676	+	TGCACCCAGACCTGGTCGTTGGG
220	Chr1:36097658-36097680	-	GCGGCCCAACGACCAGGTCTGGG
221	Chr1:36097659-36097681	-	TGCGGCCCAACGACCAGGTCTGG
222	Chr1:36097664-36097686	+	CCTGGTCGTTGGGCCGACGCTGG
223	Chr1:36097664-36097686	-	CCAGCTGCGGCCCAACGACCAGG
224	Chr1:36097671-36097693	+	GTTGGGCCGACGCTGGAGCACGG
225	Chr1:36097677-36097699	-	GTGGGGCCGTGCTCCAGCTGCGG
226	Chr1:36097688-36097710	+	GCACGGCCCCACCAGATGCCTGG
227	Chr1:36097694-36097716	+	CCCCACCAGATGCCTGGTCCAGG
228	Chr1:36097694-36097716	-	CCTGGACCAGGCATCTGGTGGGG
229	Chr1:36097695-36097717	-	ACCTGGACCAGGCATCTGGTGGG
230	Chr1:36097696-36097718	-	TACCTGGACCAGGCATCTGGTGG
231	Chr1:36097699-36097721	-	GGCTACCTGGACCAGGCATCTGG
232	Chr1:36097706-36097728	-	CAAGAAGGGCTACCTGGACCAGG
233	Chr1:36097712-36097734	-	TGAGTACAAGAAGGGCTACCTGG
234	Chr1:36097719-36097741	+	GCCCTTCTTGTAATCATCGTAGG
235	Chr1:36097720-36097742	-	ACCTACGATGAGTACAAGAAGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
236	Chr1:36097721-36097743	-	TACCTACGATGAGTACAAGAAGG
237	Chr1:36097725-36097747	+	CTTGTACTCATCGTAGGTATAGG
238	Chr1:36097728-36097750	+	GTACTCATCGTAGGTATAGGTGG
239	Chr1:36097732-36097754	+	TCATCGTAGGTATAGGTGGCCGG
240	Chr1:36097751-36097773	+	CCGGCACGTTGTTCTTGTACAGG
241	Chr1:36097751-36097773	-	CCTGTACAAGAACAACGTGCCGG
242	Chr1:36097752-36097774	+	CGGCACGTTGTTCTTGTACAGGG
243	Chr1:36097767-36097789	+	GTACAGGGCCACCCACACGTTGG
244	Chr1:36097775-36097797	-	CAAGGGCACCAACGTGTGGGTGG
245	Chr1:36097778-36097800	-	CGTCAAGGGCACCAACGTGTGGG
246	Chr1:36097779-36097801	-	ACGTCAAGGGCACCAACGTGTGG
247	Chr1:36097787-36097809	+	TGGTGCCCTTGACGTGCACATGG
248	Chr1:36097792-36097814	-	GCTTACCATGTGCACGTCAAGGG
249	Chr1:36097793-36097815	-	TGCTTACCATGTGCACGTCAAGG
250	Chr1:36097816-36097838	+	AAGTAGTAGACGCCGCCACAGG
251	Chr1:36097817-36097839	+	AGTAGTAGACGCCGCCACAGGG
252	Chr1:36097821-36097843	+	GTAGACGCCGCCACAGGGCAGG
253	Chr1:36097828-36097850	-	ATCTTCACCTGCCCTGTGGGCGG
254	Chr1:36097831-36097853	-	GGCATCTTCACCTGCCCTGTGGG
255	Chr1:36097832-36097854	-	TGGCATCTTCACCTGCCCTGTGG
256	Chr1:36097836-36097858	+	AGGGCAGGTGAAGATGCCAGTGG
257	Chr1:36097840-36097862	+	CAGGTGAAGATGCCAGTGGCTGG
258	Chr1:36097841-36097863	+	AGGTGAAGATGCCAGTGGCTGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
259	Chr1:36097852-36097874	-	AGCGGCTACAACCCAGCCACTGG
260	Chr1:36097856-36097878	+	TGGCTGGGTGTGTAGCCGCTGTGG
261	Chr1:36097870-36097892	-	ACTCTCTACAATGGCCACAGCGG
262	Chr1:36097874-36097896	+	TGTGGCCATTGTAGAGAGTCCGG
263	Chr1:36097879-36097901	-	TTTGACCGGACTCTCTACAATGG
264	Chr1:36097887-36097909	+	GAGAGTCCGGTCAAATTTACGGG
265	Chr1:36097888-36097910	+	AGAGTCCGGTCAAATTTACGGG
266	Chr1:36097893-36097915	-	GCATGCCCCGTGAAATTTGACCGG
267	Chr1:36097899-36097921	+	AAATTTACGGGCATGCCCCGAGG
268	Chr1:36097902-36097924	+	TTTCACGGGCATGCCCCGAGGCGG
269	Chr1:36097903-36097925	+	TTCACGGGCATGCCCCGAGGCGGG
270	Chr1:36097904-36097926	+	TCACGGGCATGCCCCGAGGCGGGG
271	Chr1:36097908-36097930	+	GGGCATGCCCCGAGGCGGGGAAGG
272	Chr1:36097909-36097931	+	GGCATGCCCCGAGGCGGGGAAGGG
273	Chr1:36097914-36097936	+	GCCCGAGGCGGGGAAGGGCGAGG
274	Chr1:36097915-36097937	-	ACCTCGCCCTTCCCCGCCTCGGG
275	Chr1:36097916-36097938	-	CACCTCGCCCTTCCCCGCCTCGG
276	Chr1:36097932-36097954	+	CGAGGTGAGCACCGCAGTGAAGG
277	Chr1:36097936-36097958	+	GTGAGCACCGCAGTGAAGGCCGG
278	Chr1:36097941-36097963	+	CACCGCAGTGAAGGCCGGTGTGG
279	Chr1:36097943-36097965	-	TGCCACACCGGCCTTCACTGCGG
280	Chr1:36097946-36097968	+	CAGTGAAGGCCGGTGTGGCATGG
281	Chr1:36097947-36097969	+	AGTGAAGGCCGGTGTGGCATGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
282	Chr1:36097955-36097977	-	GCTGTCTGCCCATGCCACACCGG
283	Chr1:36097975-36097997	+	AGCTCGCCCAGCCCAAACGTGTGG
284	Chr1:36097981-36098003	-	GGCAAGCCACAGTTTGGGCTGGG
285	Chr1:36097982-36098004	-	GGGCAAGCCACAGTTTGGGCTGG
286	Chr1:36097986-36098008	-	AGGGGGGCAAGCCACAGTTTGGG
287	Chr1:36097987-36098009	-	AAGGGGGGCAAGCCACAGTTTGG
288	Chr1:36097998-36098020	+	CTTGCCCCCTTGCCCAGCACGG
289	Chr1:36098002-36098024	-	GGTGCCGTGCTGGGCAAGGGGGG
290	Chr1:36098003-36098025	-	GGGTGCCGTGCTGGGCAAGGGGG
291	Chr1:36098004-36098026	-	AGGGTGCCGTGCTGGGCAAGGGG
292	Chr1:36098005-36098027	-	GAGGGTGCCGTGCTGGGCAAGGG
293	Chr1:36098006-36098028	-	GGAGGGTGCCGTGCTGGGCAAGG
294	Chr1:36098011-36098033	-	GGTGTGGAGGGTGCCGTGCTGGG
295	Chr1:36098012-36098034	-	CGGTGTGGAGGGTGCCGTGCTGG
296	Chr1:36098019-36098041	+	GGCACCCCTCCACACCGCCGTTGG
297	Chr1:36098020-36098042	+	GCACCCCTCCACACCGCCGTTGGG
298	Chr1:36098023-36098045	-	CTGCCCCAACGGCGGTGTGGAGGG
299	Chr1:36098024-36098046	+	CCTCCACACCGCCGTTGGGCAGG
300	Chr1:36098024-36098046	-	CCTGCCCCAACGGCGGTGTGGAGG
301	Chr1:36098027-36098049	-	GCACCTGCCCCAACGGCGGTGTGG
302	Chr1:36098032-36098054	-	GGCTTGCACCTGCCCCAACGGCGG
303	Chr1:36098035-36098057	-	GCAGGCTTGCACCTGCCCCAACGG
304	Chr1:36098053-36098075	-	TTCGATGAGACTGGCATCGCAGG

SEQ ID No	Chromosomal location	Strand	Target sequence
305	Chr1:36098055-36098077	+	TGCGATGCCAGTCTCATCGAAGG
306	Chr1:36098062-36098084	+	CCAGTCTCATCGAAGGCCCCAGG
307	Chr1:36098062-36098084	-	CCTGGGGCCTTCGATGAGACTGG
308	Chr1:36098063-36098085	+	CAGTCTCATCGAAGGCCCCAGGG
309	Chr1:36098064-36098086	+	AGTCTCATCGAAGGCCCCAGGGG
310	Chr1:36098071-36098093	+	TCGAAGGCCCCAGGGGCACCAGG
311	Chr1:36098072-36098094	+	CGAAGGCCCCAGGGGCACCAGGG
312	Chr1:36098073-36098095	+	GAAGGCCCCAGGGGCACCAGGGG
313	Chr1:36098074-36098096	+	AAGGCCCCAGGGGCACCAGGGGG
314	Chr1:36098078-36098100	-	GGGACCCCCTGGTGCCCCTGGGG
315	Chr1:36098079-36098101	-	CGGGACCCCCTGGTGCCCCTGGG
316	Chr1:36098080-36098102	+	CCAGGGGCACCAGGGGGTCCCGG
317	Chr1:36098080-36098102	-	CCGGGACCCCCTGGTGCCCCTGG
318	Chr1:36098081-36098103	+	CAGGGGCACCAGGGGGTCCCGGG
319	Chr1:36098082-36098104	+	AGGGGCACCAGGGGGTCCCGGGG
320	Chr1:36098083-36098105	+	GGGGCACCAGGGGGTCCCGGGGG
321	Chr1:36098088-36098110	+	ACCAGGGGGTCCCGGGGGCCCCGG
322	Chr1:36098089-36098111	+	CCAGGGGGTCCCGGGGGCCCCGGG
323	Chr1:36098089-36098111	-	CCCGGGCCCCCGGGACCCCCTGG
324	Chr1:36098092-36098114	+	GGGGGTCCCGGGGGCCCGGGAGG
325	Chr1:36098098-36098120	+	CCCGGGGGCCCCGGGAGGCCCCGG
326	Chr1:36098098-36098120	-	CCGGGGCCTCCCGGGCCCCCGGG
327	Chr1:36098099-36098121	-	TCCGGGGCCTCCCGGGCCCCCGG

SEQ ID No	Chromosomal location	Strand	Target sequence
328	Chr1:36098101-36098123	+	GGGGGCCCCGGAGGCCCCGGAGG
329	Chr1:36098102-36098124	+	GGGGCCCCGGAGGCCCCGGAGGG
330	Chr1:36098106-36098128	-	CGGGCCCTCCGGGGCCTCCCCGGG
331	Chr1:36098107-36098129	-	ACGGGCCCTCCGGGGCCTCCCCGG
332	Chr1:36098115-36098137	-	CTGGAATCACGGGCCCTCCGGGG
333	Chr1:36098116-36098138	+	CCCGAGGGCCCCGTGATTCCAGG
334	Chr1:36098116-36098138	-	CCTGGAATCACGGGCCCTCCGGG
335	Chr1:36098117-36098139	+	CCCGAGGGCCCCGTGATTCCAGGG
336	Chr1:36098117-36098139	-	CCCTGGAATCACGGGCCCTCCGG
337	Chr1:36098118-36098140	+	CGGAGGGCCCCGTGATTCCAGGGG
338	Chr1:36098125-36098147	+	CCCGTGATTCCAGGGGAGCCAGG
339	Chr1:36098125-36098147	-	CCTGGCTCCCCTGGAATCACGGG
340	Chr1:36098126-36098148	+	CCGTGATTCCAGGGGAGCCAGGG
341	Chr1:36098126-36098148	-	CCCTGGCTCCCCTGGAATCACGG
342	Chr1:36098134-36098156	+	CCAGGGGAGCCAGGGACCCCTGG
343	Chr1:36098134-36098156	-	CCAGGGGTCCCTGGCTCCCCTGG
344	Chr1:36098135-36098157	+	CAGGGGAGCCAGGGACCCCTGGG
345	Chr1:36098136-36098158	+	AGGGGAGCCAGGGACCCCTGGGG
346	Chr1:36098137-36098159	+	GGGGAGCCAGGGACCCCTGGGGG
347	Chr1:36098143-36098165	-	ACGGGGCCCCCAGGGGTCCCTGG
348	Chr1:36098145-36098167	+	AGGGACCCCTGGGGGCCCCGTGG
349	Chr1:36098146-36098168	+	GGGACCCCTGGGGGCCCCGTGGG
350	Chr1:36098150-36098172	-	TGGGCCCACGGGGCCCCCAGGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
351	Chr1:36098151-36098173	-	CTGGGCCCACGGGGCCCCCAGGG
352	Chr1:36098152-36098174	-	GCTGGGCCCACGGGGCCCCCAGG
353	Chr1:36098160-36098182	-	CTGGCACGGCTGGGCCCACGGGG
354	Chr1:36098161-36098183	+	CCCGTGGGCCCAGCCGTGCCAGG
355	Chr1:36098161-36098183	-	CCTGGCACGGCTGGGCCCACGGG
356	Chr1:36098162-36098184	-	ACCTGGCACGGCTGGGCCCACGG
357	Chr1:36098169-36098191	-	CAGGGGAACCTGGCACGGCTGGG
358	Chr1:36098170-36098192	-	GCAGGGGAACCTGGCACGGCTGG
359	Chr1:36098174-36098196	-	GAGAGCAGGGGAACCTGGCACGG
360	Chr1:36098179-36098201	-	GAGGGGAGAGCAGGGGAACCTGG
361	Chr1:36098185-36098207	+	TCCCCTGCTCTCCCCTCTCCAGG
362	Chr1:36098186-36098208	+	CCCCTGCTCTCCCCTCTCCAGGG
363	Chr1:36098186-36098208	-	CCCTGGAGAGGGGAGAGCAGGGG
364	Chr1:36098187-36098209	+	CCCTGCTCTCCCCTCTCCAGGGG
365	Chr1:36098187-36098209	-	CCCCTGGAGAGGGGAGAGCAGGG
366	Chr1:36098188-36098210	+	CCTGCTCTCCCCTCTCCAGGGGG
367	Chr1:36098188-36098210	-	CCCCCTGGAGAGGGGAGAGCAGG
368	Chr1:36098194-36098216	+	CTCCCCTCTCCAGGGGGCCCTGG
369	Chr1:36098196-36098218	-	TGCCAGGGCCCCCTGGAGAGGGG
370	Chr1:36098197-36098219	-	CTGCCAGGGCCCCCTGGAGAGGG
371	Chr1:36098198-36098220	+	CCTCTCCAGGGGGCCCTGGCAGG
372	Chr1:36098198-36098220	-	CCTGCCAGGGCCCCCTGGAGAGG
373	Chr1:36098203-36098225	+	CCAGGGGGCCCTGGCAGGCCTGG

SEQ ID No	Chromosomal location	Strand	Target sequence
374	Chr1:36098203-36098225	-	CCAGGCCTGCCAGGGCCCCCTGG
375	Chr1:36098211-36098233	-	AGGGGGAACCAGGCCTGCCAGGG
376	Chr1:36098212-36098234	-	AAGGGGGAACCAGGCCTGCCAGG
377	Chr1:36098216-36098238	+	GCAGGCCTGGTTCCCCCTCAGG
378	Chr1:36098221-36098243	+	CCTGGTTCCCCCTCAGGCCCGG
379	Chr1:36098221-36098243	-	CCGGGCCTGAAGGGGGAACCAGG
380	Chr1:36098225-36098247	+	GTTCCCCCTCAGGCCCGGCAGG
381	Chr1:36098228-36098250	-	AGGCCTGCCGGGCCTGAAGGGGG
382	Chr1:36098229-36098251	-	AAGGCCTGCCGGGCCTGAAGGGG
383	Chr1:36098230-36098252	-	CAAGGCCTGCCGGGCCTGAAGGG
384	Chr1:36098231-36098253	+	CCTTCAGGCCCGGCAGGCCTTGG
385	Chr1:36098231-36098253	-	CCAAGGCCTGCCGGGCCTGAAGG
386	Chr1:36098232-36098254	+	CTTCAGGCCCGGCAGGCCTTGGG
387	Chr1:36098233-36098255	+	TTCAGGCCCGGCAGGCCTTGGGG
388	Chr1:36098239-36098261	-	ATTGGGCCCCAAGGCCTGCCGGG
389	Chr1:36098240-36098262	-	TATTGGGCCCCAAGGCCTGCCGG
390	Chr1:36098242-36098264	+	GGCAGGCCTTGGGGCCCAATAGG
391	Chr1:36098243-36098265	+	GCAGGCCTTGGGGCCCAATAGGG
392	Chr1:36098248-36098270	-	GCTGGCCCTATTGGGGCCCAAGG
393	Chr1:36098251-36098273	+	TGGGGCCCAATAGGGCCAGCTGG
394	Chr1:36098256-36098278	-	AGGGTCCAGCTGGCCCTATTGGG
395	Chr1:36098257-36098279	-	CAGGGTCCAGCTGGCCCTATTGG
396	Chr1:36098258-36098280	+	CAATAGGGCCAGCTGGACCCTGG

SEQ ID No	Chromosomal location	Strand	Target sequence
397	Chr1:36098266-36098288	+	CCAGCTGGACCCTGGAGTCCTGG
398	Chr1:36098266-36098288	-	CCAGGACTCCAGGGTCCAGCTGG
399	Chr1:36098267-36098289	+	CAGCTGGACCCTGGAGTCCTGGG
400	Chr1:36098275-36098297	-	TCAGGAATCCCAGGACTCCAGGG
401	Chr1:36098276-36098298	-	CTCAGGAATCCCAGGACTCCAGG
402	Chr1:36098277-36098299	+	CTGGAGTCCTGGGATTCCTGAGG
403	Chr1:36098278-36098300	+	TGGAGTCCTGGGATTCCTGAGGG
404	Chr1:36098284-36098306	-	AGGGGTCCCTCAGGAATCCCAGG
405	Chr1:36098288-36098310	+	GGATTCCTGAGGGACCCCTCAGG
406	Chr1:36098293-36098315	+	CCTGAGGGACCCCTCAGGCCAGG
407	Chr1:36098293-36098315	-	CCTGGCCTGAGGGGTCCCTCAGG
408	Chr1:36098302-36098324	+	CCCCTCAGGCCAGGCTGCCCAGG
409	Chr1:36098302-36098324	-	CCTGGGCAGCCTGGCCTGAGGGG
410	Chr1:36098303-36098325	+	CCCTCAGGCCAGGCTGCCCAGGG
411	Chr1:36098303-36098325	-	CCCTGGGCAGCCTGGCCTGAGGG
412	Chr1:36098304-36098326	-	TCCCTGGGCAGCCTGGCCTGAGG
413	Chr1:36098311-36098333	-	TTGGGGCTCCCTGGGCAGCCTGG
414	Chr1:36098319-36098341	-	AAGGTGACTTGGGGCTCCCTGGG
415	Chr1:36098320-36098342	-	AAAGGTGACTTGGGGCTCCCTGG
416	Chr1:36098328-36098350	-	TGGGGCAGAAAGGTGACTTGGGG
417	Chr1:36098329-36098351	-	CTGGGGCAGAAAGGTGACTTGGG
418	Chr1:36098330-36098352	+	CCAAGTCACCTTTCTGCCCCAGG
419	Chr1:36098330-36098352	-	CCTGGGGCAGAAAGGTGACTTGG

SEQ ID No	Chromosomal location	Strand	Target sequence
420	Chr1:36098331-36098353	+	CAAGTCACCTTTCTGCCCCAGGG
421	Chr1:36098338-36098360	-	GCAGGAGCCCTGGGGCAGAAAGG
422	Chr1:36098346-36098368	-	CAGGGGTGGCAGGAGCCCTGGGG
423	Chr1:36098347-36098369	+	CCCAGGGCTCCTGCCACCCCTGG
424	Chr1:36098347-36098369	-	CCAGGGGTGGCAGGAGCCCTGGG
425	Chr1:36098348-36098370	-	ACCAGGGGTGGCAGGAGCCCTGG
426	Chr1:36098356-36098378	+	CCTGCCACCCCTGGTCCTCCAGG
427	Chr1:36098356-36098378	-	CCTGGAGGACCAGGGGTGGCAGG
428	Chr1:36098357-36098379	+	CTGCCACCCCTGGTCCTCCAGGG
429	Chr1:36098360-36098382	-	TCGCCCTGGAGGACCAGGGGTGG
430	Chr1:36098363-36098385	-	GGGTCGCCCTGGAGGACCAGGGG
431	Chr1:36098364-36098386	-	CGGGTCGCCCTGGAGGACCAGGG
432	Chr1:36098365-36098387	-	ACGGGTTCGCCCTGGAGGACCAGG
433	Chr1:36098371-36098393	-	GGTTTCACGGGTTCGCCCTGGAGG
434	Chr1:36098374-36098396	+	CCAGGGCGACCCGTGAAACCCGG
435	Chr1:36098374-36098396	-	CCGGGTTCACGGGTTCGCCCTGG
436	Chr1:36098383-36098405	-	AAGGGTGAGCCGGGTTCACGGG
437	Chr1:36098384-36098406	-	CAAGGGTGAGCCGGGTTCACGG
438	Chr1:36098385-36098407	+	CGTGAAACCCGGCTCACCCCTGG
439	Chr1:36098386-36098408	+	GTGAAACCCGGCTCACCCCTGGG
440	Chr1:36098392-36098414	-	ACTGGGCCCCAAGGGTGAGCCGGG
441	Chr1:36098393-36098415	-	AACTGGGCCCCAAGGGTGAGCCGG
442	Chr1:36098395-36098417	+	GGCTCACCCCTGGGCCCAGTTGG

SEQ ID No	Chromosomal location	Strand	Target sequence
443	Chr1:36098401-36098423	+	CCCTTGGGCCCAGTTGGTCCAGG
444	Chr1:36098401-36098423	-	CCTGGACCAACTGGGCCCCAAGGG
445	Chr1:36098402-36098424	+	CCTTGGGCCCAGTTGGTCCAGGG
446	Chr1:36098402-36098424	-	CCCTGGACCAACTGGGCCCCAAGG
447	Chr1:36098403-36098425	+	CTTGGGCCCAGTTGGTCCAGGGG
448	Chr1:36098404-36098426	+	TTGGGCCCAGTTGGTCCAGGGGG
449	Chr1:36098409-36098431	-	ATGGACCCCCTGGACCAACTGGG
450	Chr1:36098410-36098432	-	CATGGACCCCCTGGACCAACTGG
451	Chr1:36098411-36098433	+	CAGTTGGTCCAGGGGGTCCATGG
452	Chr1:36098412-36098434	+	AGTTGGTCCAGGGGGTCCATGGG
453	Chr1:36098419-36098441	+	CCAGGGGGTCCATGGGCCCCAGG
454	Chr1:36098419-36098441	-	CCTGGGGCCCATGGACCCCCTGG
455	Chr1:36098428-36098450	-	AGGGGACTTCCTGGGGCCCATGG
456	Chr1:36098435-36098457	-	AGGTGAGAGGGGACTTCCTGGGG
457	Chr1:36098436-36098458	-	CAGGTGAGAGGGGACTTCCTGGG
458	Chr1:36098437-36098459	+	CCAGGAAGTCCCCTCTCACCTGG
459	Chr1:36098437-36098459	-	CCAGGTGAGAGGGGACTTCCTGG
460	Chr1:36098438-36098460	+	CAGGAAGTCCCCTCTCACCTGGG
461	Chr1:36098446-36098468	+	CCCCTCTCACCTGGGACCCCTGG
462	Chr1:36098446-36098468	-	CCAGGGGTCCCAGGTGAGAGGGG
463	Chr1:36098447-36098469	-	ACCAGGGGTCCCAGGTGAGAGGG
464	Chr1:36098448-36098470	-	AACCAGGGGTCCCAGGTGAGAGG
465	Chr1:36098455-36098477	-	GCTGGGAAACCAGGGGTCCCAGG

SEQ ID No	Chromosomal location	Strand	Target sequence
466	Chr1:36098459-36098481	+	GGACCCCTGGTTTCCCAGCCAGG
467	Chr1:36098462-36098484	-	TGGCCTGGCTGGGAAACCAGGGG
468	Chr1:36098463-36098485	-	GTGGCCTGGCTGGGAAACCAGGG
469	Chr1:36098464-36098486	-	AGTGGCCTGGCTGGGAAACCAGG
470	Chr1:36098467-36098489	+	GGTTTCCCAGCCAGGCCACTAGG
471	Chr1:36098472-36098494	-	AGGGGCCTAGTGGCCTGGCTGGG
472	Chr1:36098473-36098495	-	CAGGGGCCTAGTGGCCTGGCTGG
473	Chr1:36098474-36098496	+	CAGCCAGGCCACTAGGCCCTGG
474	Chr1:36098477-36098499	-	TGACCAGGGGCCTAGTGGCCTGG
475	Chr1:36098482-36098504	-	CGAGGTGACCAGGGGCCTAGTGG
476	Chr1:36098490-36098512	-	CTGGCATTGAGGTGACCAGGGG
477	Chr1:36098491-36098513	+	CCCTGGTCACCTCGAATGCCAGG
478	Chr1:36098491-36098513	-	CCTGGCATTGAGGTGACCAGGG
479	Chr1:36098492-36098514	-	GCCTGGCATTGAGGTGACCAGG
480	Chr1:36098500-36098522	+	CCTCGAATGCCAGGCACTCCTGG
481	Chr1:36098500-36098522	-	CCAGGAGTGCCTGGCATTGAGG
482	Chr1:36098501-36098523	+	CTCGAATGCCAGGCACTCCTGGG
483	Chr1:36098502-36098524	+	TCGAATGCCAGGCACTCCTGGGG
484	Chr1:36098503-36098525	+	CGAATGCCAGGCACTCCTGGGGG
485	Chr1:36098509-36098531	-	GGAGGACCCCCAGGAGTGCCTGG
486	Chr1:36098512-36098534	+	GGCACTCCTGGGGGTCCTCCAGG
487	Chr1:36098518-36098540	-	GCAGGGCCTGGAGGACCCCCAGG
488	Chr1:36098527-36098549	-	AAGGCTGAGGCAGGGCCTGGAGG

SEQ ID No	Chromosomal location	Strand	Target sequence
489	Chr1:36098530-36098552	+	CCAGGCCCTGCCTCACCCCTTAGG
490	Chr1:36098530-36098552	-	CCTAAGGGTGAGGCAGGGCCTGG
491	Chr1:36098535-36098557	-	CTGGGCCTAAGGGTGAGGCAGGG
492	Chr1:36098536-36098558	+	CCTGCCTCACCCCTTAGGCCAGG
493	Chr1:36098536-36098558	-	CCTGGGCCTAAGGGTGAGGCAGG
494	Chr1:36098537-36098559	+	CTGCCTCACCCCTTAGGCCAGGG
495	Chr1:36098538-36098560	+	TGCCTCACCCCTTAGGCCAGGGG
496	Chr1:36098539-36098561	+	GCCTCACCCCTTAGGCCAGGGGG
497	Chr1:36098540-36098562	-	GCCCCCTGGGCCTAAGGGTGAGG
498	Chr1:36098545-36098567	-	CGTGGGCCCCCTGGGCCTAAGGG
499	Chr1:36098546-36098568	-	ACGTGGGCCCCCTGGGCCTAAGG
500	Chr1:36098553-36098575	-	CTGGCAGACGTGGGCCCCCTGGG
501	Chr1:36098554-36098576	+	CCAGGGGGCCACGTCTGCCAGG
502	Chr1:36098554-36098576	-	CCTGGCAGACGTGGGCCCCCTGG
503	Chr1:36098562-36098584	-	CAGGGCTTCCTGGCAGACGTGGG
504	Chr1:36098563-36098585	-	GCAGGGCTTCCTGGCAGACGTGG
505	Chr1:36098572-36098594	+	CCAGGAAGCCCTGCAGACCCAGG
506	Chr1:36098572-36098594	-	CCTGGGTCTGCAGGGCTTCCTGG
507	Chr1:36098580-36098602	-	CTGGACTTCCTGGGTCTGCAGGG
508	Chr1:36098581-36098603	+	CCTGCAGACCCAGGAAGTCCAGG
509	Chr1:36098581-36098603	-	CCTGGACTTCCTGGGTCTGCAGG
510	Chr1:36098582-36098604	+	CTGCAGACCCAGGAAGTCCAGGG
511	Chr1:36098583-36098605	+	TGCAGACCCAGGAAGTCCAGGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
512	Chr1:36098584-36098606	+	GCAGACCCAGGAAGTCCAGGGGG
513	Chr1:36098589-36098611	-	GGGGTCCCCCTGGACTTCCTGGG
514	Chr1:36098590-36098612	-	GGGGGTCCCCCTGGACTTCCTGG
515	Chr1:36098599-36098621	-	CAGGGTCTTGGGGGTCCCCCTGG
516	Chr1:36098602-36098624	+	GGGGGACCCCCAAGACCCTGTGG
517	Chr1:36098603-36098625	+	GGGGACCCCCAAGACCCTGTGGG
518	Chr1:36098608-36098630	-	CAGGGCCCACAGGGTCTTGGGGG
519	Chr1:36098609-36098631	-	GCAGGGCCCACAGGGTCTTGGGG
520	Chr1:36098610-36098632	-	AGCAGGGCCCACAGGGTCTTGGG
521	Chr1:36098611-36098633	-	GAGCAGGGCCCACAGGGTCTTGG
522	Chr1:36098617-36098639	+	CCCTGTGGGCCCTGCTCCCCTGG
523	Chr1:36098617-36098639	-	CCAGGGGAGCAGGGCCCACAGGG
524	Chr1:36098618-36098640	-	GCCAGGGGAGCAGGGCCCACAGG
525	Chr1:36098626-36098648	-	GATGGGGAGCCAGGGGAGCAGGG
526	Chr1:36098627-36098649	-	GGATGGGGAGCCAGGGGAGCAGG
527	Chr1:36098633-36098655	-	AGGGGAGGATGGGGAGCCAGGGG
528	Chr1:36098634-36098656	-	CAGGGGAGGATGGGGAGCCAGGG
529	Chr1:36098635-36098657	+	CCTGGCTCCCCATCCTCCCCTGG
530	Chr1:36098635-36098657	-	CCAGGGGAGGATGGGGAGCCAGG
531	Chr1:36098642-36098664	-	GGGTGAGCCAGGGGAGGATGGGG
532	Chr1:36098643-36098665	-	GGGGTGAGCCAGGGGAGGATGGG
533	Chr1:36098644-36098666	-	AGGGGTGAGCCAGGGGAGGATGG
534	Chr1:36098648-36098670	-	GGACAGGGGTGAGCCAGGGGAGG

SEQ ID No	Chromosomal location	Strand	Target sequence
535	Chr1:36098651-36098673	-	GGGGGACAGGGGTGAGCCAGGGG
536	Chr1:36098652-36098674	-	TGGGGGACAGGGGTGAGCCAGGG
537	Chr1:36098653-36098675	-	TTGGGGGACAGGGGTGAGCCAGG
538	Chr1:36098662-36098684	+	CCCCTGTCCCCCAAGAGTCCTGG
539	Chr1:36098662-36098684	-	CCAGGACTCTTGGGGGACAGGGG
540	Chr1:36098663-36098685	+	CCCTGTCCCCCAAGAGTCCTGGG
541	Chr1:36098663-36098685	-	CCCAGGACTCTTGGGGGACAGGG
542	Chr1:36098664-36098686	-	TCCCAGGACTCTTGGGGGACAGG
543	Chr1:36098669-36098691	-	TGGGGTCCCAGGACTCTTGGGGG
544	Chr1:36098670-36098692	-	CTGGGGTCCCAGGACTCTTGGGG
545	Chr1:36098671-36098693	-	GCTGGGGTCCCAGGACTCTTGGG
546	Chr1:36098672-36098694	-	AGCTGGGGTCCCAGGACTCTTGG
547	Chr1:36098674-36098696	+	AAGAGTCCTGGGACCCCAGCTGG
548	Chr1:36098675-36098697	+	AGAGTCCTGGGACCCCAGCTGGG
549	Chr1:36098680-36098702	-	AGGGGCCAGCTGGGGTCCCAGG
550	Chr1:36098687-36098709	-	GGGGGACAGGGGCCAGCTGGGG
551	Chr1:36098688-36098710	-	AGGGGGACAGGGGCCAGCTGGG
552	Chr1:36098689-36098711	-	AAGGGGGACAGGGGCCAGCTGG
553	Chr1:36098691-36098713	+	AGCTGGGGCCCCTGTCCCCCTTGG
554	Chr1:36098692-36098714	+	GCTGGGGCCCCTGTCCCCCTTGGG
555	Chr1:36098693-36098715	+	CTGGGGCCCCTGTCCCCCTTGGGG
556	Chr1:36098698-36098720	+	CCCCTGTCCCCCTTGGGGCCTGG
557	Chr1:36098698-36098720	-	CCAGGCCCCAAGGGGGACAGGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
558	Chr1:36098699-36098721	-	GCCAGGCCCCAAGGGGGACAGGG
559	Chr1:36098700-36098722	-	TGCCAGGCCCCAAGGGGGACAGG
560	Chr1:36098705-36098727	-	AGGACTGCCAGGCCCCAAGGGGG
561	Chr1:36098706-36098728	-	CAGGACTGCCAGGCCCCAAGGGG
562	Chr1:36098707-36098729	+	CCCTTGGGGCCTGGCAGTCCTGG
563	Chr1:36098707-36098729	-	CCAGGACTGCCAGGCCCCAAGGG
564	Chr1:36098708-36098730	-	GCCAGGACTGCCAGGCCCCAAGG
565	Chr1:36098716-36098738	-	TATGGGATGCCAGGACTGCCAGG
566	Chr1:36098724-36098746	+	TCCTGGCATCCCATAGCCAGTGG
567	Chr1:36098725-36098747	+	CCTGGCATCCCATAGCCAGTGGG
568	Chr1:36098725-36098747	-	CCCACTGGCTATGGGATGCCAGG
569	Chr1:36098726-36098748	+	CTGGCATCCCATAGCCAGTGGGG
570	Chr1:36098733-36098755	-	TGATAGGCCCCACTGGCTATGGG
571	Chr1:36098734-36098756	-	CTGATAGGCCCCACTGGCTATGG
572	Chr1:36098740-36098762	+	CCAGTGGGGCCTATCAGCCCAGG
573	Chr1:36098740-36098762	-	CCTGGGCTGATAGGCCCCACTGG
574	Chr1:36098741-36098763	+	CAGTGGGGCCTATCAGCCCAGGG
575	Chr1:36098742-36098764	+	AGTGGGGCCTATCAGCCCAGGGG
576	Chr1:36098743-36098765	+	GTGGGGCCTATCAGCCCAGGGGG
577	Chr1:36098744-36098766	+	TGGGGCCTATCAGCCCAGGGGGG
578	Chr1:36098749-36098771	-	CGGGGCCCCCTGGGCTGATAGG
579	Chr1:36098750-36098772	+	CTATCAGCCCAGGGGGGCCCCGG
580	Chr1:36098751-36098773	+	TATCAGCCCAGGGGGGCCCCGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
581	Chr1:36098757-36098779	-	CAGGGACCCGGGGCCCCCTGGG
582	Chr1:36098758-36098780	+	CCAGGGGGGGCCCCGGGTCCCTGG
583	Chr1:36098758-36098780	-	CCAGGGACCCGGGGCCCCCTGG
584	Chr1:36098767-36098789	-	AAAGGGGAGCCAGGGACCCGGGG
585	Chr1:36098768-36098790	-	CAAAGGGGAGCCAGGGACCCGGG
586	Chr1:36098769-36098791	+	CCGGGTCCCTGGCTCCCCTTTGG
587	Chr1:36098769-36098791	-	CCAAAGGGGAGCCAGGGACCCGG
588	Chr1:36098775-36098797	-	CAGGGGCCAAAGGGGAGCCAGGG
589	Chr1:36098776-36098798	-	TCAGGGGCCAAAGGGGAGCCAGG
590	Chr1:36098779-36098801	+	GGCTCCCCTTTGGCCCCTGATGG
591	Chr1:36098780-36098802	+	GCTCCCCTTTGGCCCCTGATGGG
592	Chr1:36098783-36098805	-	GGGCCCATCAGGGGGCCAAAGGGG
593	Chr1:36098784-36098806	-	AGGGCCCATCAGGGGGCCAAAGGG
594	Chr1:36098785-36098807	-	CAGGGCCCATCAGGGGGCCAAAGG
595	Chr1:36098788-36098810	+	TTGGCCCCTGATGGGCCCTGTGG
596	Chr1:36098792-36098814	-	AGGACCACAGGGCCCATCAGGGG
597	Chr1:36098793-36098815	-	CAGGACCACAGGGCCCATCAGGG
598	Chr1:36098794-36098816	+	CCTGATGGGCCCTGTGGTCCTGG
599	Chr1:36098794-36098816	-	CCAGGACCACAGGGCCCATCAGG
600	Chr1:36098803-36098825	-	GCAGGGTTGCCAGGACCACAGGG
601	Chr1:36098804-36098826	-	AGCAGGGTTGCCAGGACCACAGG
602	Chr1:36098812-36098834	+	CCTGGCAACCCTGCTGCCCCTGG
603	Chr1:36098812-36098834	-	CCAGGGGCAGCAGGGTTGCCAGG

SEQ ID No	Chromosomal location	Strand	Target sequence
604	Chr1:36098813-36098835	+	CTGGCAACCCTGCTGCCCCTGGG
605	Chr1:36098820-36098842	-	TGGGAGTCCCAGGGGCAGCAGGG
606	Chr1:36098821-36098843	-	GTGGGAGTCCCAGGGGCAGCAGG
607	Chr1:36098828-36098850	-	AGACGGTGTGGGAGTCCCAGGGG
608	Chr1:36098829-36098851	-	TAGACGGTGTGGGAGTCCCAGGG
609	Chr1:36098830-36098852	-	GTAGACGGTGTGGGAGTCCCAGG
610	Chr1:36098836-36098858	+	ACTCCCACACCGTCTACTCCAGG
611	Chr1:36098839-36098861	+	CCCACACCGTCTACTCCAGGAGG
612	Chr1:36098839-36098861	-	CCTCCTGGAGTAGACGGTGTGGG
613	Chr1:36098840-36098862	-	ACCTCCTGGAGTAGACGGTGTGG
614	Chr1:36098845-36098867	-	AAAGGACCTCCTGGAGTAGACGG
615	Chr1:36098848-36098870	+	TCTACTCCAGGAGGTCCTTTTGG
616	Chr1:36098849-36098871	+	CTACTCCAGGAGGTCCTTTTGGG
617	Chr1:36098854-36098876	-	GTGGGCCCCAAAAGGACCTCCTGG
618	Chr1:36098863-36098885	+	CCTTTTTGGGCCCACAGCTCCTGG
619	Chr1:36098863-36098885	-	CCAGGAGCTGTGGGCCCCAAAAGG
620	Chr1:36098872-36098894	-	AGGGGGGAGCCAGGAGCTGTGGG
621	Chr1:36098873-36098895	-	CAGGGGGGAGCCAGGAGCTGTGG
622	Chr1:36098874-36098896	+	CACAGCTCCTGGCTCCCCCCTGG
623	Chr1:36098875-36098897	+	ACAGCTCCTGGCTCCCCCCTGGG
624	Chr1:36098876-36098898	+	CAGCTCCTGGCTCCCCCCTGGGG
625	Chr1:36098881-36098903	+	CCTGGCTCCCCCCTGGGGCCTGG
626	Chr1:36098881-36098903	-	CCAGGCCCCAGGGGGGAGCCAGG

SEQ ID No	Chromosomal location	Strand	Target sequence
627	Chr1:36098888-36098910	-	TGGAGTTCCAGGCCCCAGGGGGG
628	Chr1:36098889-36098911	-	CTGGAGTTCCAGGCCCCAGGGGGG
629	Chr1:36098890-36098912	+	CCCCTGGGGCCTGGAAGTCCAGG
630	Chr1:36098890-36098912	-	CCTGGAGTTCCAGGCCCCAGGGGG
631	Chr1:36098891-36098913	-	TCCTGGAGTTCCAGGCCCCAGGG
632	Chr1:36098892-36098914	-	CTCCTGGAGTTCCAGGCCCCAGG
633	Chr1:36098893-36098915	+	CTGGGGCCTGGAAGTCCAGGAGG
634	Chr1:36098899-36098921	-	TCTGGGCCTCCTGGAGTTCCAGG
635	Chr1:36098908-36098930	-	AAGGGTGAGTCTGGGCCTCCTGG
636	Chr1:36098916-36098938	-	CAGGAGACAAGGGTGAGTCTGGG
637	Chr1:36098917-36098939	+	CCAGACTCACCTTGTCTCCTGG
638	Chr1:36098917-36098939	-	CCAGGAGACAAGGGTGAGTCTGG
639	Chr1:36098918-36098940	+	CAGACTCACCTTGTCTCCTGGG
640	Chr1:36098919-36098941	+	AGACTCACCTTGTCTCCTGGGG
641	Chr1:36098926-36098948	+	CCCTTGTCTCCTGGGGCCCCAGG
642	Chr1:36098926-36098948	-	CCTGGGGCCCCAGGAGACAAGGG
643	Chr1:36098927-36098949	-	TCCTGGGGCCCCAGGAGACAAGG
644	Chr1:36098935-36098957	-	GATGGGCTTCCTGGGGCCCCAGG
645	Chr1:36098942-36098964	-	TGGTTTGGATGGGCTTCCTGGGG
646	Chr1:36098943-36098965	-	CTGGTTTGGATGGGCTTCCTGGG
647	Chr1:36098944-36098966	+	CCAGGAAGCCCATCCAAACCAGG
648	Chr1:36098944-36098966	-	CCTGGTTTGGATGGGCTTCCTGG
649	Chr1:36098952-36098974	-	TAGGCAAACCTGGTTTGGATGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
650	Chr1:36098953-36098975	-	TTAGGCAAACCTGGTTTGGATGG
651	Chr1:36098957-36098979	-	TGGCTTAGGCAAACCTGGTTTGG
652	Chr1:36098962-36098984	+	CCAGGTTTGCCTAAGCCAGCTGG
653	Chr1:36098962-36098984	-	CCAGCTGGCTTAGGCAAACCTGG
654	Chr1:36098968-36098990	+	TTGCCTAAGCCAGCTGGACCAGG
655	Chr1:36098969-36098991	+	TGCCTAAGCCAGCTGGACCAGGG
656	Chr1:36098971-36098993	-	CTCCCTGGTCCAGCTGGCTTAGG
657	Chr1:36098972-36098994	+	CTAAGCCAGCTGGACCAGGGAGG
658	Chr1:36098976-36098998	+	GCCAGCTGGACCAGGGAGGCCGG
659	Chr1:36098977-36098999	+	CCAGCTGGACCAGGGAGGCCGGG
660	Chr1:36098977-36098999	-	CCCGGCCTCCCTGGTCCAGCTGG
661	Chr1:36098978-36099000	+	CAGCTGGACCAGGGAGGCCGGGG
662	Chr1:36098979-36099001	+	AGCTGGACCAGGGAGGCCGGGGG
663	Chr1:36098980-36099002	+	GCTGGACCAGGGAGGCCGGGGGG
664	Chr1:36098981-36099003	+	CTGGACCAGGGAGGCCGGGGGGG
665	Chr1:36098985-36099007	+	ACCAGGGAGGCCGGGGGGGGCCGG
666	Chr1:36098986-36099008	+	CCAGGGAGGCCGGGGGGGGCCGGG
667	Chr1:36098986-36099008	-	CCCGGCCCCCCCCGGCCTCCCTGG
668	Chr1:36098987-36099009	+	CAGGGAGGCCGGGGGGGGCCGGGG
669	Chr1:36098988-36099010	+	AGGGAGGCCGGGGGGGGCCGGGGG
670	Chr1:36098995-36099017	-	GGGGGTGCCCCCGCCCCCCCCGG
671	Chr1:36099004-36099026	+	CCGGGGGACCCCCCTGCCCTGG
672	Chr1:36099004-36099026	-	CCAGGGCAGGGGGGTGCCCCCGG

SEQ ID No	Chromosomal location	Strand	Target sequence
673	Chr1:36099005-36099027	+	CGGGGGCACCCCCCTGCCCTGGG
674	Chr1:36099006-36099028	+	GGGGGCACCCCCCTGCCCTGGGG
675	Chr1:36099013-36099035	+	CCCCCCTGCCCTGGGGCCCCAGG
676	Chr1:36099013-36099035	-	CCTGGGGCCCCAGGGCAGGGGGG
677	Chr1:36099014-36099036	-	GCCTGGGGCCCCAGGGCAGGGGG
678	Chr1:36099015-36099037	-	TGCCTGGGGCCCCAGGGCAGGGG
679	Chr1:36099016-36099038	-	CTGCCTGGGGCCCCAGGGCAGGG
680	Chr1:36099017-36099039	-	GCTGCCTGGGGCCCCAGGGCAGG
681	Chr1:36099021-36099043	+	CCCTGGGGCCCCAGGCAGCCCGG
682	Chr1:36099021-36099043	-	CCGGGCTGCCTGGGGCCCCAGGG
683	Chr1:36099022-36099044	+	CCTGGGGCCCCAGGCAGCCCGGG
684	Chr1:36099022-36099044	-	CCCGGGCTGCCTGGGGCCCCAGG
685	Chr1:36099026-36099048	+	GGGCCCCAGGCAGCCCGGGCTGG
686	Chr1:36099029-36099051	-	GGGCCAGCCCGGGCTGCCTGGGG
687	Chr1:36099030-36099052	-	TGGGCCAGCCCGGGCTGCCTGGG
688	Chr1:36099031-36099053	-	GTGGGCCAGCCCGGGCTGCCTGG
689	Chr1:36099039-36099061	-	ATAATGGAGTGGGCCAGCCCGGG
690	Chr1:36099040-36099062	-	GATAATGGAGTGGGCCAGCCCGG
691	Chr1:36099049-36099071	-	CTCAAGGGGGATAATGGAGTGGG
692	Chr1:36099050-36099072	+	CCACTCCATTATCCCCCTTGAGG
693	Chr1:36099050-36099072	-	CCTCAAGGGGGATAATGGAGTGG
694	Chr1:36099055-36099077	-	CGAGGCCTCAAGGGGGATAATGG
695	Chr1:36099062-36099084	-	AGGTGATCGAGGCCTCAAGGGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
696	Chr1:36099063-36099085	-	CAGGTGATCGAGGCCTCAAGGGG
697	Chr1:36099064-36099086	+	CCCTTGAGGCCTCGATCACCTGG
698	Chr1:36099064-36099086	-	CCAGGTGATCGAGGCCTCAAGGG
699	Chr1:36099065-36099087	+	CCTTGAGGCCTCGATCACCTGGG
700	Chr1:36099065-36099087	-	CCCAGGTGATCGAGGCCTCAAGG
701	Chr1:36099066-36099088	+	CTTGAGGCCTCGATCACCTGGGG
702	Chr1:36099067-36099089	+	TTGAGGCCTCGATCACCTGGGGG
703	Chr1:36099073-36099095	+	CCTCGATCACCTGGGGGCCAGG
704	Chr1:36099073-36099095	-	CCTGGGGCCCCAGGTGATCGAGG
705	Chr1:36099082-36099104	-	CAGGGGGAGCCTGGGGCCCCCAGG
706	Chr1:36099083-36099105	+	CTGGGGGGCCCAGGCTCCCCCTGG
707	Chr1:36099084-36099106	+	TGGGGGGCCCAGGCTCCCCCTGGG
708	Chr1:36099085-36099107	+	GGGGGGCCCAGGCTCCCCCTGGGG
709	Chr1:36099090-36099112	-	CAGGGCCCCAGGGGGAGCCTGGG
710	Chr1:36099091-36099113	+	CCAGGCTCCCCCTGGGGGCCCTGG
711	Chr1:36099091-36099113	-	CCAGGGCCCCAGGGGGAGCCTGG
712	Chr1:36099098-36099120	-	GGGGGAACCAGGGCCCCAGGGGG
713	Chr1:36099099-36099121	-	AGGGGGAACCAGGGCCCCAGGGG
714	Chr1:36099100-36099122	-	CAGGGGGAACCAGGGCCCCAGGG
715	Chr1:36099101-36099123	+	CCTGGGGCCCTGGTTCCCCCTGG
716	Chr1:36099101-36099123	-	CCAGGGGGAACCAGGGCCCCAGG
717	Chr1:36099108-36099130	-	CAGGATTCCAGGGGGAACCAGGG
718	Chr1:36099109-36099131	+	CCTGGTTCCCCCTGGAATCCTGG

SEQ ID No	Chromosomal location	Strand	Target sequence
719	Chr1:36099109-36099131	-	CCAGGATTCCAGGGGGAACCAGG
720	Chr1:36099110-36099132	+	CTGGTTCCCCCTGGAATCCTGGG
721	Chr1:36099111-36099133	+	TGGTTCCCCCTGGAATCCTGGGG
722	Chr1:36099112-36099134	+	GGTTCCCCCTGGAATCCTGGGG
723	Chr1:36099116-36099138	-	AGGGCCCCCAGGATTCCAGGGG
724	Chr1:36099117-36099139	-	CAGGGCCCCCAGGATTCCAGGGG
725	Chr1:36099118-36099140	+	CCCTGGAATCCTGGGGGGCCCTG
726	Chr1:36099118-36099140	-	CCAGGGCCCCCAGGATTCCAGG
727	Chr1:36099119-36099141	-	GCCAGGGCCCCCAGGATTCCAG
728	Chr1:36099127-36099149	-	CAAGGGGTGCCAGGGCCCCCAGG
729	Chr1:36099128-36099150	+	CTGGGGGGCCCTGGCACCCCTTGG
730	Chr1:36099129-36099151	+	TGGGGGGCCCTGGCACCCCTTGGG
731	Chr1:36099135-36099157	-	CAGGTGCCCAAGGGGTGCCAGGG
732	Chr1:36099136-36099158	+	CCTGGCACCCCTTGGGCACCTGG
733	Chr1:36099136-36099158	-	CCAGGTGCCCAAGGGGTGCCAGG
734	Chr1:36099143-36099165	-	TGGAAAACCAGGTGCCCAAGGGG
735	Chr1:36099144-36099166	-	CTGGAAAACCAGGTGCCCAAGGG
736	Chr1:36099145-36099167	+	CCTTGGGCACCTGGTTTTCAGG
737	Chr1:36099145-36099167	-	CCTGGAAAACCAGGTGCCCAAG
738	Chr1:36099146-36099168	+	CTTGGGCACCTGGTTTTCAGGG
739	Chr1:36099154-36099176	-	ATTACTATCCCTGGAAAACCAGG
740	Chr1:36099162-36099184	+	TCCAGGGATAGTAATGCCTGAG
741	Chr1:36099163-36099185	+	CCAGGGATAGTAATGCCTGAGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
742	Chr1:36099163-36099185	-	CCCTCAGGCATTACTATCCCTGG
743	Chr1:36099164-36099186	+	CAGGGATAGTAATGCCTGAGGGG
744	Chr1:36099169-36099191	+	ATAGTAATGCCTGAGGGGCCCCGG
745	Chr1:36099170-36099192	+	TAGTAATGCCTGAGGGGCCCCGGG
746	Chr1:36099173-36099195	+	TAATGCCTGAGGGGCCCCGGGAGG
747	Chr1:36099178-36099200	+	CCTGAGGGGCCCCGGGAGGCCAGG
748	Chr1:36099178-36099200	-	CCTGGCCTCCCCGGGCCCCCTCAGG
749	Chr1:36099179-36099201	+	CTGAGGGGCCCCGGGAGGCCAGGG
750	Chr1:36099180-36099202	+	TGAGGGGCCCCGGGAGGCCAGGGG
751	Chr1:36099181-36099203	+	GAGGGGCCCCGGGAGGCCAGGGGG
752	Chr1:36099187-36099209	+	CCCGGGAGGCCAGGGGGTCTCTGG
753	Chr1:36099187-36099209	-	CCAGGACCCCCTGGCCTCCCCGGG
754	Chr1:36099188-36099210	+	CCGGGAGGCCAGGGGGTCTCTGGG
755	Chr1:36099188-36099210	-	CCCAGGACCCCCTGGCCTCCCCGG
756	Chr1:36099189-36099211	+	CGGGAGGCCAGGGGGTCTCTGGGG
757	Chr1:36099190-36099212	+	GGGAGGCCAGGGGGTCTCTGGGGG
758	Chr1:36099196-36099218	-	CGGGGACCCCCAGGACCCCCTG
759	Chr1:36099197-36099219	+	CAGGGGGTCTCTGGGGGTCCCCGG
760	Chr1:36099200-36099222	+	GGGGTCTCTGGGGGTCCCCGGAGG
761	Chr1:36099205-36099227	-	CAGGGCCTCCGGGGACCCCCAGG
762	Chr1:36099206-36099228	+	CTGGGGGTCCCCGGAGGCCCTGG
763	Chr1:36099214-36099236	-	CGAGGGGACCAGGGCCTCCGGGG
764	Chr1:36099215-36099237	-	ACGAGGGGACCAGGGCCTCCGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
765	Chr1:36099216-36099238	-	TACGAGGGGACCAGGGCCTCCGG
766	Chr1:36099223-36099245	+	CCCTGGTCCCCTCGTATTCCTGG
767	Chr1:36099223-36099245	-	CCAGGAATACGAGGGGACCAGGG
768	Chr1:36099224-36099246	-	GCCAGGAATACGAGGGGACCAGG
769	Chr1:36099230-36099252	-	GGGGGAGCCAGGAATACGAGGGG
770	Chr1:36099231-36099253	-	GGGGGGAGCCAGGAATACGAGGG
771	Chr1:36099232-36099254	-	CGGGGGGAGCCAGGAATACGAGG
772	Chr1:36099241-36099263	+	CCTGGCTCCCCCGAAGCCCCGG
773	Chr1:36099241-36099263	-	CCGGGGCTTCGGGGGAGCCAGG
774	Chr1:36099248-36099270	-	AGGGCAGCCGGGGCTTCGGGGGG
775	Chr1:36099249-36099271	-	CAGGGCAGCCGGGGCTTCGGGGG
776	Chr1:36099250-36099272	+	CCCCGAAGCCCCGGCTGCCCTGG
777	Chr1:36099250-36099272	-	CCAGGGCAGCCGGGGCTTCGGGG
778	Chr1:36099251-36099273	-	ACCAGGGCAGCCGGGGCTTCGGG
779	Chr1:36099252-36099274	-	CACCAGGGCAGCCGGGGCTTCGG
780	Chr1:36099253-36099275	+	CGAAGCCCCGGCTGCCCTGGTGG
781	Chr1:36099258-36099280	-	TCGGGCCACCAGGGCAGCCGGGG
782	Chr1:36099259-36099281	-	GTCGGGCCACCAGGGCAGCCGGG
783	Chr1:36099260-36099282	-	GGTCGGGCCACCAGGGCAGCCGG
784	Chr1:36099267-36099289	-	CTGGCAAGGTCGGGCCACCAGGG
785	Chr1:36099268-36099290	+	CCTGGTGGCCCGACCTTGCCAGG
786	Chr1:36099268-36099290	-	CCTGGCAAGGTCGGGCCACCAGG
787	Chr1:36099269-36099291	+	CTGGTGGCCCGACCTTGCCAGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
788	Chr1:36099276-36099298	-	CAGGGCTCCCTGGCAAGGTCGGG
789	Chr1:36099277-36099299	+	CCGACCTTGCCAGGGAGCCCTGG
790	Chr1:36099277-36099299	-	CCAGGGCTCCCTGGCAAGGTCGG
791	Chr1:36099278-36099300	+	CGACCTTGCCAGGGAGCCCTGGG
792	Chr1:36099279-36099301	+	GACCTTGCCAGGGAGCCCTGGGG
793	Chr1:36099280-36099302	+	ACCTTGCCAGGGAGCCCTGGGGG
794	Chr1:36099281-36099303	-	TCCCCCAGGGCTCCCTGGCAAGG
795	Chr1:36099286-36099308	-	GCTGGTCCCCCAGGGCTCCCTGG
796	Chr1:36099294-36099316	-	TGGGCAAGGCTGGTCCCCCAGGG
797	Chr1:36099295-36099317	-	ATGGGCAAGGCTGGTCCCCCAGG
798	Chr1:36099299-36099321	+	GGGACCAGCCTTGCCCATCCGG
799	Chr1:36099300-36099322	+	GGGACCAGCCTTGCCCATCCGGG
800	Chr1:36099304-36099326	-	TTCTCCCGGATGGGCAAGGCTGG
801	Chr1:36099308-36099330	-	TGGCTTCTCCCGGATGGGCAAGG
802	Chr1:36099310-36099332	+	TTGCCCATCCGGGAGAAGCCAGG
803	Chr1:36099311-36099333	+	TGCCCATCCGGGAGAAGCCAGGG
804	Chr1:36099312-36099334	+	GCCCATCCGGGAGAAGCCAGGGG
805	Chr1:36099313-36099335	+	CCCATCCGGGAGAAGCCAGGGGG
806	Chr1:36099313-36099335	-	CCCCCTGGCTTCTCCCGGATGGG
807	Chr1:36099314-36099336	-	GCCCCCTGGCTTCTCCCGGATGG
808	Chr1:36099318-36099340	-	CTGGGCCCCCTGGCTTCTCCCGG
809	Chr1:36099322-36099344	+	GAGAAGCCAGGGGGCCAGCAGG
810	Chr1:36099323-36099345	+	AGAAGCCAGGGGGCCAGCAGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
811	Chr1:36099328-36099350	+	CCAGGGGGGCCAGCAGGGCCAGG
812	Chr1:36099328-36099350	-	CCTGGCCCTGCTGGGCCCCCTGG
813	Chr1:36099336-36099358	-	ATGGGCAGCCTGGCCCTGCTGGG
814	Chr1:36099337-36099359	-	CATGGGCAGCCTGGCCCTGCTGG
815	Chr1:36099338-36099360	+	CAGCAGGGGCCAGGCTGCCCATGG
816	Chr1:36099346-36099368	+	CCAGGCTGCCCATGGAGTCCTGG
817	Chr1:36099346-36099368	-	CCAGGACTCCATGGGCAGCCTGG
818	Chr1:36099354-36099376	-	TGGGAAAGCCAGGACTCCATGGG
819	Chr1:36099355-36099377	-	ATGGGAAAGCCAGGACTCCATGG
820	Chr1:36099361-36099383	+	AGTCCTGGCTTTCCCATGCCTGG
821	Chr1:36099364-36099386	-	AAACCAGGCATGGGAAAGCCAGG
822	Chr1:36099370-36099392	+	TTTCCCATGCCTGGTTTTCTCTGG
823	Chr1:36099371-36099393	+	TTCCCATGCCTGGTTTTCTCTGGG
824	Chr1:36099373-36099395	-	TTCCCAGGAAAACCAGGCATGGG
825	Chr1:36099374-36099396	-	CTTCCCAGGAAAACCAGGCATGG
826	Chr1:36099379-36099401	+	CCTGGTTTTCTCTGGGAAGCCAGG
827	Chr1:36099379-36099401	-	CCTGGCTTCCCAGGAAAACCAGG
828	Chr1:36099380-36099402	+	CTGGTTTTCTCTGGGAAGCCAGGG
829	Chr1:36099381-36099403	+	TGGTTTTCTCTGGGAAGCCAGGGG
830	Chr1:36099382-36099404	+	GGTTTTCTCTGGGAAGCCAGGGGG
831	Chr1:36099383-36099405	+	GTTTTCTCTGGGAAGCCAGGGGGG
832	Chr1:36099388-36099410	+	CCTGGGAAGCCAGGGGGGCCAGG
833	Chr1:36099388-36099410	-	CCTGGCCCCCTGGCTTCCCAGG

SEQ ID No	Chromosomal location	Strand	Target sequence
834	Chr1:36099389-36099411	+	CTGGGAAGCCAGGGGGGCCAGGG
835	Chr1:36099390-36099412	+	TGGGAAGCCAGGGGGGCCAGGGG
836	Chr1:36099391-36099413	+	GGGAAGCCAGGGGGGCCAGGGGG
837	Chr1:36099397-36099419	-	CGGGGTCCCCCTGGCCCCCTGG
838	Chr1:36099400-36099422	+	GGGGGGCCAGGGGGACCCCGAGG
839	Chr1:36099405-36099427	+	GCCAGGGGGACCCCGAGGCCCGG
840	Chr1:36099406-36099428	+	CCAGGGGGACCCCGAGGCCCGGG
841	Chr1:36099406-36099428	-	CCCGGGCCTCGGGGTCCCCCTGG
842	Chr1:36099415-36099437	+	CCCCGAGGCCCGGGCTTCCCAGG
843	Chr1:36099415-36099437	-	CCTGGGAAGCCCGGGCCTCGGGG
844	Chr1:36099416-36099438	+	CCCGAGGCCCGGGCTTCCCAGGG
845	Chr1:36099416-36099438	-	CCCTGGGAAGCCCGGGCCTCGGG
846	Chr1:36099417-36099439	+	CCGAGGCCCGGGCTTCCCAGGGG
847	Chr1:36099417-36099439	-	CCCCTGGGAAGCCCGGGCCTCGG
848	Chr1:36099418-36099440	+	CGAGGCCCGGGCTTCCCAGGGGG
849	Chr1:36099419-36099441	+	GAGGCCCGGGCTTCCCAGGGGGG
850	Chr1:36099423-36099445	+	CCCGGGCTTCCCAGGGGGGCCGG
851	Chr1:36099423-36099445	-	CCGGCCCCCTGGGAAGCCCGGG
852	Chr1:36099424-36099446	+	CCGGGCTTCCCAGGGGGGCCGGG
853	Chr1:36099424-36099446	-	CCCGGCCCCCTGGGAAGCCCGG
854	Chr1:36099432-36099454	-	AGGGAGAGCCCGGCCCCCTGGG
855	Chr1:36099433-36099455	-	AAGGGAGAGCCCGGCCCCCTGG
856	Chr1:36099437-36099459	+	GGGGGCCGGGCTCTCCCTCAGG

SEQ ID No	Chromosomal location	Strand	Target sequence
857	Chr1:36099442-36099464	-	ATGGACCTGAAGGGAGAGCCCGG
858	Chr1:36099445-36099467	+	GGCTCTCCCTTCAGGTCCATCGG
859	Chr1:36099451-36099473	-	CTGCTGCCGATGGACCTGAAGGG
860	Chr1:36099452-36099474	-	GCTGCTGCCGATGGACCTGAAGG
861	Chr1:36099454-36099476	+	TTCAGGTCCATCGGCAGCAGCGG
862	Chr1:36099460-36099482	+	TCCATCGGCAGCAGCGGTAGAGG
863	Chr1:36099461-36099483	-	GCCTCTACCGCTGCTGCCGATGG
864	Chr1:36099485-36099507	+	TTTCTGAGAAAGAAAGAGAAAGG
865	Chr1:36099486-36099508	+	TTCTGAGAAAGAAAAGAGAAAGGG
866	Chr1:36099487-36099509	+	TCTGAGAAAGAAAAGAGAAAGGGG
867	Chr1:36099495-36099517	+	AGAAAGAGAAAGGGGCAGTCAGG
868	Chr1:36099496-36099518	+	GAAAGAGAAAGGGGCAGTCAGGG
869	Chr1:36099497-36099519	+	AAAGAGAAAGGGGCAGTCAGGGG
870	Chr1:36099509-36099531	+	GCAGTCAGGGGCCTGAACTGTGG
871	Chr1:36099510-36099532	+	CAGTCAGGGGCCTGAACTGTGGG
872	Chr1:36099511-36099533	+	AGTCAGGGGCCTGAACTGTGGGG
873	Chr1:36099516-36099538	+	GGGGCCTGAACTGTGGGGACAGG
874	Chr1:36099517-36099539	+	GGGCCTGAACTGTGGGGACAGGG
875	Chr1:36099518-36099540	+	GGCCTGAACTGTGGGGACAGGGG
876	Chr1:36099520-36099542	-	GTCCCCTGTCCCCACAGTTCAGG
877	Chr1:36099542-36099564	-	AATGGGGGAATGGGTAGATGGGG
878	Chr1:36099543-36099565	-	GAATGGGGGAATGGGTAGATGGG
879	Chr1:36099544-36099566	-	GGAATGGGGGAATGGGTAGATGG

SEQ ID No	Chromosomal location	Strand	Target sequence
880	Chr1:36099551-36099573	-	TCATACTGGAATGGGGGAATGGG
881	Chr1:36099552-36099574	-	CTCATACTGGAATGGGGGAATGG
882	Chr1:36099553-36099575	+	CATTCCCCCATCCACTATGAGG
883	Chr1:36099557-36099579	-	TGTACCTCATACTGGAATGGGGG
884	Chr1:36099558-36099580	-	GTGTACCTCATACTGGAATGGGG
885	Chr1:36099559-36099581	-	CGTGTACCTCATACTGGAATGGG
886	Chr1:36099560-36099582	+	CCATTCCAGTATGAGGTACACGG
887	Chr1:36099560-36099582	-	CCGIGTACCTCATACTGGAATGG
888	Chr1:36099561-36099583	+	CATTCCAGTATGAGGTACACGGG
889	Chr1:36099565-36099587	-	CTCICCCGTGTACCTCATACTGG
890	Chr1:36099566-36099588	+	CAGTATGAGGTACACGGGAGAGG
891	Chr1:36099574-36099596	+	GGTACACGGGAGAGGAAGAATGG
892	Chr1:36099575-36099597	+	GTACACGGGAGAGGAAGAATGGG
893	Chr1:36099576-36099598	+	TACACGGGAGAGGAAGAATGGGG
894	Chr1:36099598-36099620	+	GCTGCCCCCTTCCTGCTCTCATGG
895	Chr1:36099602-36099624	-	TCTTCCATGAGAGCAGGAAGGGG
896	Chr1:36099603-36099625	-	ATCTTCCATGAGAGCAGGAAGGG
897	Chr1:36099604-36099626	-	CATCTTCCATGAGAGCAGGAAGG
898	Chr1:36099605-36099627	+	CTTCCTGCTCTCATGGAAGATGG
899	Chr1:36099606-36099628	+	TTCTGCTCTCATGGAAGATGGG
900	Chr1:36099607-36099629	+	TCCTGCTCTCATGGAAGATGGGG
901	Chr1:36099608-36099630	-	ACCCCATCTTCCATGAGAGCAGG
902	Chr1:36099612-36099634	+	CTCTCATGGAAGATGGGCTTTGG

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SEQ ID No	Chromosomal location	Strand	Target sequence
903	Chr1:36099613-36099635	+	TCTCATGGAAGATGGGGTTTGGG
904	Chr1:36099614-36099636	+	CTCATGGAAGATGGGGTTTGGGG
905	Chr1:36099615-36099637	+	TCATGGAAGATGGGGTTTGGGGG
906	Chr1:36099618-36099640	+	TGGAAGATGGGGTTTGGGGGTGG
907	Chr1:36099624-36099646	+	ATGGGGTTTGGGGGTGGCCCAGG
908	Chr1:36099625-36099647	+	TGGGGTTTGGGGGTGGCCCAGGG
909	Chr1:36099626-36099648	+	GGGGTTTGGGGGTGGCCCAGGGG
910	Chr1:36099635-36099657	+	GGGTGGCCCAGGGGACATCTTGG
911	Chr1:36099636-36099658	+	GGTGGCCCAGGGGACATCTTGGG
912	Chr1:36099637-36099659	+	GTGGCCCAGGGGACATCTTGGGG
913	Chr1:36099638-36099660	+	TGGCCCAGGGGACATCTTGGGGG
914	Chr1:36099641-36099663	-	TTGCCCCCAAGATGTCCCCTGGG
915	Chr1:36099642-36099664	-	GTTGCCCCCAAGATGTCCCCTGG
916	Chr1:36099645-36099667	+	GGGGACATCTTGGGGGCAACAGG
917	Chr1:36099646-36099668	+	GGGACATCTTGGGGGCAACAGGG
918	Chr1:36099660-36099682	+	GCAACAGGGTGTCTCTCTTAAGG
919	Chr1:36099661-36099683	+	CAACAGGGTGTCTCTCTTAAGGG
920	Chr1:36099672-36099694	-	GGTGTTAGGAGCCCTTAAGGAGG
921	Chr1:36099675-36099697	-	TTGGGTGTTAGGAGCCCTTAAGG
922	Chr1:36099685-36099707	+	TCCTAACACCCAACCTACCTAGG
923	Chr1:36099686-36099708	-	GCCTAGGTAGGTGGGTGTTAGG
924	Chr1:36099689-36099711	+	AACACCCAACCTACCTAGGCTGG
925	Chr1:36099690-36099712	+	ACACCCAACCTACCTAGGCTGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
926	Chr1:36099693-36099715	-	AGGCCCAGCCTAGGTAGGTTGGG
927	Chr1:36099694-36099716	-	GAGGCCCAGCCTAGGTAGGTTGG
928	Chr1:36099698-36099720	-	GGAGGAGGCCCAGCCTAGGTAGG
929	Chr1:36099702-36099724	-	TCATGGAGGAGGCCCAGCCTAGG
930	Chr1:36099708-36099730	+	CTGGGCCTCCTCCATGAGCCTGG
931	Chr1:36099713-36099735	-	ATCAGCCAGGCTCATGGAGGAGG
932	Chr1:36099716-36099738	-	AGAATCAGCCAGGCTCATGGAGG
933	Chr1:36099719-36099741	-	GTGAGAATCAGCCAGGCTCATGG
934	Chr1:36099726-36099748	-	ATGAGAGGTGAGAATCAGCCAGG
935	Chr1:36099741-36099763	-	TCAGGTCATGCAGGGATGAGAGG
936	Chr1:36099744-36099766	+	CTCATCCCTGCATGACCTGAAGG
937	Chr1:36099747-36099769	+	ATCCCTGCATGACCTGAAGGTGG
938	Chr1:36099749-36099771	-	CTCCACCTTCAGGTCATGCAGGG
939	Chr1:36099750-36099772	-	ACTCCACCTTCAGGTCATGCAGG
940	Chr1:36099752-36099774	+	TGCATGACCTGAAGGTGGAGTGG
941	Chr1:36099759-36099781	-	CTGGTGGCCACTCCACCTTCAGG
942	Chr1:36099760-36099782	+	CTGAAGGTGGAGTGGCCACCAGG
943	Chr1:36099763-36099785	+	AAGGTGGAGTGGCCACCAGGTGG
944	Chr1:36099775-36099797	-	GGGCTGCTGGTGCCACCTGGTGG
945	Chr1:36099778-36099800	-	GGTGGGCTGCTGGTGCCACCTGG
946	Chr1:36099788-36099810	-	CGGGCTCTAAGGTGGGCTGCTGG
947	Chr1:36099791-36099813	+	GCAGCCCACCTTAGAGCCCGTGG
948	Chr1:36099792-36099814	+	CAGCCCACCTTAGAGCCCGTGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
949	Chr1:36099795-36099817	-	GCTCCACGGGCTCTAAGGTGGG
950	Chr1:36099796-36099818	-	TGCTCCACGGGCTCTAAGGTGG
951	Chr1:36099799-36099821	-	CTCTGCTCCACGGGCTCTAAGG
952	Chr1:36099807-36099829	-	AGGTGGGGCTCTGCTCCACGGG
953	Chr1:36099808-36099830	-	GAGGTGGGGCTCTGCTCCACGG
954	Chr1:36099822-36099844	-	AACTGGGAAGTTGGGAGGTGGGG
955	Chr1:36099823-36099845	-	GAACTGGGAAGTTGGGAGGTGGG
956	Chr1:36099824-36099846	-	TGAACTGGGAAGTTGGGAGGTGG
957	Chr1:36099827-36099849	-	AGATGAACTGGGAAGTTGGGAGG
958	Chr1:36099830-36099852	-	GGGAGATGAACTGGGAAGTTGGG
959	Chr1:36099831-36099853	-	GGGGAGATGAACTGGGAAGTTGG
960	Chr1:36099836-36099858	+	TTCCCAGTTCATCTCCCCCTTGG
961	Chr1:36099838-36099860	-	TTCCAAGGGGGAGATGAACTGGG
962	Chr1:36099839-36099861	-	CTTCCAAGGGGGAGATGAACTGG
963	Chr1:36099850-36099872	-	GCACAGGTGGTCTTCCAAGGGGG
964	Chr1:36099851-36099873	-	GGCACAGGTGGTCTTCCAAGGGG
965	Chr1:36099852-36099874	-	TGGCACAGGTGGTCTTCCAAGGG
966	Chr1:36099853-36099875	-	CTGGCACAGGTGGTCTTCCAAGG
967	Chr1:36099863-36099885	-	GTGCAGTTAGCTGGCACAGGTGG
968	Chr1:36099866-36099888	-	ACGGTGCAGTTAGCTGGCACAGG
969	Chr1:36099872-36099894	-	CTGGAAACGGTGCAGTTAGCTGG
970	Chr1:36099873-36099895	+	CAGCTAACTGCACCGTTTCCAGG
971	Chr1:36099881-36099903	+	TGCACCGTTTCCAGGCCCTCTGG

SEQ ID No	Chromosomal location	Strand	Target sequence
972	Chr1:36099882-36099904	+	GCACCGTTTCCAGGCCCTCTGGG
973	Chr1:36099883-36099905	+	CACCGTTTCCAGGCCCTCTGGGG
974	Chr1:36099885-36099907	-	TACCCAGAGGGCCTGGAAACGG
975	Chr1:36099890-36099912	+	TCCAGGCCCTCTGGGGTATTAGG
976	Chr1:36099891-36099913	-	TCCTAATAACCCAGAGGGCCTGG
977	Chr1:36099896-36099918	-	GTTTTCCTAATAACCCAGAGGG
978	Chr1:36099897-36099919	-	TGTTTTCCTAATAACCCAGAGG
979	Chr1:36099904-36099926	+	GGTATTAGGAAAAACACTGAAGG
980	Chr1:36099908-36099930	+	TIAGGAAAAACACTGAAGGCTAGG
981	Chr1:36099916-36099938	+	AACACTGAAGGCTAGGAAAATTGG
982	Chr1:36099919-36099941	+	ACTGAAGGTAAGGAAAATTGGTGG
983	Chr1:36099920-36099942	+	CTGAAGGCTAGGAAAATTGGTGGG
984	Chr1:36099921-36099943	+	TGAAGGCTAGGAAAATTGGTGGGG
985	Chr1:36099928-36099950	+	AGGAAAATTGCTGGGGAATGAGG
986	Chr1:36099936-36099958	+	TGGTGGGGAATGAGGAGCTGTGG
987	Chr1:36099939-36099961	+	TGGGGAATGAGGAGCTGTGGAGG
988	Chr1:36099940-36099962	+	GGGGAATGAGGAGCTGTGGAGGG
989	Chr1:36099949-36099971	+	GGAGCTGTGGAGGGCGCCTGAGG
990	Chr1:36099958-36099980	+	GAGGGCGCCTGAGGATCTGATGG
991	Chr1:36099965-36099987	-	CTGAGAGCCATCAGATCCTCAGG
992	Chr1:36099966-36099988	+	CTGAGGATCTGATGGCTCTCAGG
993	Chr1:36099967-36099989	+	TGAGGATCTGATGGCTCTCAGGG
994	Chr1:36099970-36099992	+	CGATCTGATGGCTCTCAGGGAGG

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SEQ ID No	Chromosomal location	Strand	Target sequence
995	Chr1:36099974-36099996	+	CTGATGGCTCTCAGGGAGGCAGG
996	Chr1:36099975-36099997	+	TGATGGCTCTCAGGGAGGCAGGG
997	Chr1:36099976-36099998	+	GATGGCTCTCAGGGAGGCAGGGG
998	Chr1:36099982-36100004	+	TCTCAGGGAGGCAGGGGATTTGG
999	Chr1:36099983-36100005	+	CTCAGGGAGGCAGGGGATTTGGG
1000	Chr1:36099984-36100006	+	TCAGGGAGGCAGGGGATTTGGGG
1001	Chr1:36099985-36100007	+	CAGGGAGGCAGGGGATTTGGGGG
1002	Chr1:36099989-36100011	+	GAGGCAGGGGATTTGGGGGCTGG
1003	Chr1:36099990-36100012	+	AGGCAGGGGATTTGGGGGCTGGG
1004	Chr1:36100002-36100024	+	TGGGGGCTGGGAGCGATTTGAGG
1005	Chr1:36100010-36100032	+	GGGAGCGATTTGAGGCACTGTGG
1006	Chr1:36100011-36100033	+	GGAGCGATTTGAGGCACTGTGGG
1007	Chr1:36100012-36100034	+	GAGCGATTTGAGGCACTGTGGGG
1008	Chr1:36100017-36100039	+	ATTTGAGGCACTGTGGGGTGAGG
1009	Chr1:36100020-36100042	+	TGAGGCACTGTGGGGTGAGGAGG
1010	Chr1:36100032-36100054	+	GGGTGAGGAGGCTCTCACCCAGG
1011	Chr1:36100038-36100060	+	GGAGGCTCTCACCCAGGTACTGG
1012	Chr1:36100049-36100071	-	GAGGGCAAAGGCCAGTACCTGGG
1013	Chr1:36100050-36100072	-	TGAGGGCAAAGGCCAGTACCTGG
1014	Chr1:36100053-36100075	+	GGTACTGGCCTTTGCCCTCACGG
1015	Chr1:36100057-36100079	+	CTGGCCTTTGCCCTCACGGAAGG
1016	Chr1:36100058-36100080	+	TGGCCTTTGCCCTCACGGAAGGG
1017	Chr1:36100061-36100083	+	CCTTTGCCCTCACGGAAGGGCGG

SEQ ID No	Chromosomal location	Strand	Target sequence
1018	Chr1:36100061-36100083	-	CCGCCCTTCCGTGAGGGCAAAGG
1019	Chr1:36100067-36100089	-	GTGGGACCGCCCTTCCGTGAGGG
1020	Chr1:36100068-36100090	-	TGTGGGACCGCCCTTCCGTGAGG
1021	Chr1:36100070-36100092	+	TCACGGAAGGGCGGTCCCACAGG
1022	Chr1:36100084-36100106	+	TCCCACAGGTCCTTTCTGCATGG
1023	Chr1:36100085-36100107	+	CCCACAGGTCCTTTCTGCATGGG
1024	Chr1:36100085-36100107	-	CCCATGCAGAAAGGACCTGTGGG
1025	Chr1:36100086-36100108	-	GCCCATGCAGAAAGGACCTGTGG
1026	Chr1:36100089-36100111	+	CAGGTCCTTTCTGCATGGGCTGG
1027	Chr1:36100094-36100116	-	TACATCCAGCCCATGCAGAAAGG
1028	Chr1:36100103-36100125	+	ATGGGCTGGATGTACTTCACTGG
1029	Chr1:36100104-36100126	+	TGGGCTGGATGTACTTCACTGGG
1030	Chr1:36100105-36100127	+	GGGCTGGATGTACTTCACTGGGG
1031	Chr1:36100126-36100148	+	GGCATAGCCCGCCGCCCCACCGG
1032	Chr1:36100133-36100155	-	GGCGGGGCCGGTGGGGCGGCGGG
1033	Chr1:36100134-36100156	-	TGGCGGGGCCGGTGGGGCGGCGG
1034	Chr1:36100137-36100159	-	TGGTGGCGGGGCCGGTGGGGCGG
1035	Chr1:36100140-36100162	-	CTCTGGTGGCGGGGCCGGTGGGG
1036	Chr1:36100141-36100163	+	CCCACCGGCCCCGCCACCAGAGG
1037	Chr1:36100141-36100163	-	CCTCTGGTGGCGGGGCCGGTGGG
1038	Chr1:36100142-36100164	-	TCCTCTGGTGGCGGGGCCGGTGG
1039	Chr1:36100145-36100167	-	GCGTCCTCTGGTGGCGGGGCCGG
1040	Chr1:36100149-36100171	-	GCGGGCGTCCTCTGGTGGCGGGG

SEQ ID No	Chromosomal location	Strand	Target sequence
1041	Chr1:36100150-36100172	-	CGCGGGCGTCCTCTGGTGGCGGG
1042	Chr1:36100151-36100173	+	CCGCCACCAGAGGACGCCCCGCGG
1043	Chr1:36100151-36100173	-	CCGCGGGCGTCCTCTGGTGGCGGG
1044	Chr1:36100154-36100176	-	GGGCCGCGGGCGTCCTCTGGTGG
1045	Chr1:36100157-36100179	-	TGTGGGCCGCGGGCGTCCTCTGG
1046	Chr1:36100167-36100189	-	GGTGCTGGGGTGTGGGCCGCGGG
1047	Chr1:36100168-36100190	-	TGGTGCTGGGGTGTGGGCCGCGGG
1048	Chr1:36100174-36100196	-	TGGTGCTGGTGCTGGGGTGTGGG
1049	Chr1:36100175-36100197	-	CTGGTGCTGGTGCTGGGGTGTGG
1050	Chr1:36100180-36100202	-	TGCTACTGGTGCTGGTGCTGGGG
1051	Chr1:36100181-36100203	-	CTGCTACTGGTGCTGGTGCTGGG
1052	Chr1:36100182-36100204	-	GCTGCTACTGCTACTGGTGCTGG
1053	Chr1:36100188-36100210	-	GCTGCTGCTGCTACTGGTGCTGG
1054	Chr1:36100194-36100216	-	TTCGCTGCTGCTGCTGCTACTGG
1055	Chr1:36100200-36100222	+	GCAGCAGCAGCAGCGAAGACAGG
1056	Chr1:36100201-36100223	+	CAGCAGCAGCAGCGAAGACAGGG
1057	Chr1:36100202-36100224	+	AGCAGCAGCAGCGAAGACAGGGG
1058	Chr1:36100222-36100244	+	GGGTGTCAGAGTCCCCAGCATGG
1059	Chr1:36100231-36100253	+	AGTCCCCAGCATGGCGTCCGTGG
1060	Chr1:36100234-36100256	-	CGTCCACGGACGCCATGCTGGGG
1061	Chr1:36100235-36100257	-	ACGTCCACGGACGCCATGCTGGG
1062	Chr1:36100236-36100258	-	CACGTCCACGGACGCCATGCTGG
1063	Chr1:36100248-36100270	-	TCTTCTTTGCAGCACGTCCACGG

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Table 4. Target sequences for *COL8A2* with Gln455Lys mutation

SEQ ID No	Target location	Target strand	Target sequence
1064	Chr1:36098302-36098324	+	CCCCTCAGGCCAGGCTTCCCAGG
1065	Chr1:36098302-36098324	-	CCTGGGAAGCCTGGCCTGAGGGG
1066	Chr1:36098303-36098325	+	CCCTCAGGCCAGGTTGCCAGGG
1067	Chr1:36098303-36098325	-	CCCTGGGAAGCCTGGCCTGAGGG
1068	Chr1:36098304-36098326	-	TCCCTGGGAAGCCTGGCCTGAGG
1069	Chr1:36098311-36098333	-	TTGGGGCTCCCTGGGAAGCCTGG

Table 5. Target sequences for *COL8A2* with Gln455Val mutation

SEQ ID No	Target location	Target strand	Target sequence
1070	Chr1:36098302-36098324	+	CCCCTCAGGCCAGGCACCCCAGG
1071	Chr1:36098302-36098324	-	CCTGGGGTGCCTGGCCTGAGGGG
1072	Chr1:36098303-36098325	+	CCCTCAGGCCAGGCACCCCAGGG
1073	Chr1:36098303-36098325	-	CCCTGGGGTGCCTGGCCTGAGGG
1074	Chr1:36098304-36098326	-	TCCCTGGGGTGCCTGGCCTGAGG
1075	Chr1:36098311-36098333	-	TTGGGGCTCCCTGGGGTGCCTGG

Table 6. Target sequences for *COL8A2* with Leu450Trp mutation

SEQ ID No	Target location	Target strand	Target sequence
1076	Chr1:36098311-36098333	-	TGGGGGCTCCCTGGGCAGCCTGG
1077	Chr1:36098319-36098341	-	AAGGTGACTGGGGGCTCCCTGGG
1078	Chr1:36098320-36098342	-	AAAGGTGACTGGGGGCTCCCTGG

SEQ ID No	Target location	Target strand	Target sequence
1079	Chr1:36098328-36098350	-	TGGGGCAGAAAGGTGACTGGGGG
1080	Chr1:36098329-36098351	-	CTGGGGCAGAAAGGTGACTGGGG
1081	Chr1:36098330-36098352	+	CCCAGTCACCTTTCTGCCCCAGG
1082	Chr1:36098330-36098352	-	CCTGGGGCAGAAAGGTGACTGGG
1083	Chr1:36098331-36098353	+	CCAGTCACCTTTCTGCCCCAGGG
1084	Chr1:36098331-36098353	-	CCCTGGGGCAGAAAGGTGACTGG

CLAIMS

1. A composition comprising:
 - a) a nucleotide sequence, or portion thereof, of an AAV vector; and
 - b) a nucleic acid editing system comprising at least one nucleotide sequence that is complementary to at least one mutant allele on a target gene associated with diseases or conditions in the cornea; a nucleic acid capable of down-regulating gene expression of at least one mutant allele on a target gene associated with diseases or conditions in the cornea; and/or at least one nucleotide sequence, or portion thereof, that codes for a protein to be expressed in the eye.
2. The composition of claim 1, wherein said protein is preferentially expressed in an anterior portion of the eye as compared with other ocular tissues or cells.
3. The composition of claim 1, wherein said protein is preferentially expressed in the cornea as compared with other ocular tissues or cells.
4. The composition of claim 4, wherein the protein is a transcription factor, a collagen, a nuclease, or a fluorescent protein.
5. The composition of claim 4, wherein the protein is transcription factor 4 (TCF4).
6. The composition of claim 1, wherein the nucleic acid editing system is a CRISPR system.
7. The composition of claim 1 wherein the nucleic acid editing system is a CRISPR-Cas system.
8. The composition of claim 1, wherein the CRISPR-Cas system comprises a nucleotide sequence encoding a CRISPR-associated (Cas) gene and a nucleotide sequence encoding a guide RNA (gRNA).
9. The composition of claim 1, wherein the CRISPR-Cas system is a CRISPR-Cas9 system.

10. The composition of claim 1, wherein the nucleotide sequence that is complementary to at least one mutant allele is a gRNA.
11. The composition of claim 1, wherein the at least one nucleotide sequence that is complementary to at least one mutant allele on a target gene is selected from an siRNA, an shRNA, an miRNA, an antisense RNA, or an antagomir RNA.
12. The composition of claim 1, wherein the mutant allele is encoded by a target sequence on the target gene.
13. The composition of claim 1, wherein the at least one nucleotide sequence that is complementary to at least one mutant allele on a target gene hybridizes to a target sequence on the target gene in a cell in the subject.
14. The composition of claim 1, wherein the target gene is *TCF4* or *COL8A2*.
15. The composition of claim 1, wherein at least one target sequence is selected from the group consisting of SEQ ID NOs: 1-1084.
16. The composition of claim 1, wherein at least one target sequence is specific to the *TCF4* gene, and the target sequence is selected from SEQ ID NOs: 1-190.
17. The composition of claim 1, wherein the target sequence is specific to the *COL8A2* gene and the target sequence is selected from SEQ ID NOs: 191-1084.
18. The composition of claim 1, wherein at least one guide RNA comprises a crRNA sequence that is complementary to at least one target sequence selected from SEQ ID NOs: 1-1084.
19. The composition of claim 1, wherein at least one guide RNA comprises a guide sequence selected from the group consisting of SEQ ID NOs: 1089-1278.

20. The composition of claim 1, wherein the editing system further comprises a repair template.
21. The composition of claim 20, wherein the repair template is selected from the group consisting of a DNA repair template, an mRNA repair template, an siRNA repair template, an miRNA repair template, and an antisense oligonucleotide repair template.
22. The composition of claim 1, wherein the AAV vector serotype is selected from the group consisting of AAV5, AAV6, and AAV8.
23. The composition of claim 1, wherein the AAV vector serotype is AAV5.
24. The composition of claim 1, wherein the AAV vector serotype is AAV6.
25. The composition of claim 1, wherein the AAV vector serotype is AAV8.
26. The composition of claim 1, wherein the composition further comprises a promoter.
27. The composition of claim 24, wherein the promoter is optimized for use with an AAV5, AAV6, or AAV8 vector.
28. The composition of claim 27, wherein the promoter is tissue specific, and when operably linked with the AAV vector or the nucleotide that is a sequence that is complementary to at least one mutant allele on a target gene is active in the eye.
29. The composition of claim 28, wherein the tissue specific promoter is active in the cornea.
30. The composition of claim 28, wherein the tissue specific promoter is active in the endothelium of the cornea.
31. The composition of claim 1, wherein the target gene is preferentially expressed in the anterior portion of the eye after intracameral (IC) injection.

32. The composition of claim 1, wherein the disease or condition of the cornea is a superficial corneal dystrophy, anterior corneal dystrophy, corneal stromal dystrophy, or posterior cornea dystrophy.
33. The composition of claim 1, wherein the disease or condition of the cornea is a posterior corneal dystrophy.
34. The composition of claim 32, wherein the posterior corneal dystrophy is selected from the group consisting of: Fuchs endothelial corneal dystrophy (FECD; both early and late onset), posterior polymorphous dystrophy (PPCD; types 1, 2, and 3), congenital endothelial dystrophy (types 1 and 2), and X-linked endothelial corneal dystrophy.
35. The composition of claim 34, wherein the corneal dystrophy is FECD.
36. The composition of claim 1, wherein said protein is preferentially expressed in a posterior portion of the eye as compared with other ocular tissues or cells.
37. The composition of claim 36, wherein the AAV vector serotype is selected from the group consisting of AAV2 and AAV9.
38. A method expressing a protein in an eye of a subject in need thereof comprising:
a) providing one or more adeno-associated (AAV) vectors comprising a nucleotide sequence that encodes said protein; and
b) administering the AAV vector to the eye.
39. The method of claim 38, wherein said protein is preferentially expressed in an anterior portion of the eye as compared with other parts of the eye.
40. The method of claim 39, wherein said protein is preferentially expressed in the cornea as compared with other tissues or cells in the eye.

41. The method of claim 40, wherein said protein is preferentially expressed in the endothelial cells of the cornea as compared with other tissues or cells in the eye.
42. The method of claim 41, wherein the AAV vector serotype is selected from the group consisting of AAV5, AAV6, and AAV8.
43. The method of claim 42, wherein the AAV vector serotype is AAV5.
44. The method of claim 42, wherein the AAV vector serotype is AAV6.
45. The method of claim 42, wherein the AAV vector serotype is AAV8.
46. The method of claim 38, wherein the protein is a Cas protein.
47. The method of claim 46, wherein the protein is Cas9.
48. The method of claim 38, wherein the protein is a transcription factor, a collagen, a nuclease, or a fluorescent protein.
49. The method of claim 38, wherein the protein is transcription factor 4 (TCF4).
50. The method of claim 38, wherein the vector further comprises a repair template.
51. The method of claim 50, wherein the repair template is selected from the group consisting of a DNA repair template, an mRNA repair template, an siRNA repair template, an miRNA repair template, and an antisense oligonucleotide repair template.
52. The method of claim 50, wherein the vector further comprises a promoter.
53. The method of claim 52, wherein the promoter is optimized for use with an AAV5, AAV6, or AAV8 vector.

54. The method of claim 52, wherein the promoter is tissue specific, and when operably linked with the AAV vector or the nucleotide that is a sequence that is complementary to at least one mutant allele on a target gene is active in the eye.
55. The method of claim 52, wherein the tissue specific promoter is active in the cornea.
56. The method of claim 52, wherein the tissue specific promoter is active in the endothelium of the cornea.
57. The method of claim 38, wherein the vector is administered to the subject via injection into the eye.
58. The method of claim 57, wherein the vector is administered to the subject via injection to the anterior portion of the eye.
59. The method of claim 57, wherein the vector is administered to the corneal stroma, corneal limbus, onto the epithelial surface of the cornea, or onto the endothelial membrane of the cornea
60. The method of claim 57, wherein the vector is administered to the subject via intracameral (IC) injection.
61. The method of claim 38, wherein the protein is preferentially expressed in the cornea as compared with other eye tissues or cells after IC injection.
62. The method of claim 38, wherein the protein is preferentially expressed in the corneal endothelial cells as compared with eye tissues or cells after IC injection.
63. The method of claim 38 which is suitable for treating a disease or condition in the eye.
64. The method of claim 63, wherein the disease or condition in the eye is a disease or condition of the cornea.

65. The method of claim 64, wherein the disease or condition of the cornea is a superficial corneal dystrophy, anterior corneal dystrophy, corneal stromal dystrophy, or posterior cornea dystrophy.
66. The method of claim 65, wherein the disease or condition of the cornea is a posterior corneal dystrophy.
67. The method of claim 66, wherein the posterior corneal dystrophy is Fuchs endothelial corneal dystrophy (FECD; both early and late onset), posterior polymorphous dystrophy (PPCD; types 1, 2, and 3), congenital endothelial dystrophy (types 1 and 2), and X-linked endothelial corneal dystrophy.
68. The method of claim 67, wherein the corneal dystrophy is FECD.
69. The method of claim 38, wherein said protein is preferentially expressed in a posterior portion of the eye as compared with other parts of the eye.
70. The method of claim 69, wherein the AAV vector serotype is selected from the group consisting of AAV2 and AAV9.
71. A method for repairing a gene expressed in the cornea in a subject in need thereof, the method comprising:
- a) providing a delivery system comprising a nucleic acid editing system comprising at least one nucleotide sequence that is complementary to at least one mutant allele on a target gene associated with diseases or conditions in the cornea; and
 - b) administering the delivery system to the cornea of the subject.
72. The method of claim 71, wherein the nucleic acid editing system is a CRISPR-Cas system.
73. The method of claim 72, wherein the CRISPR-Cas system is a CRISPR-Cas9 system.

74. The method of claim 71, wherein the nucleotide sequence that is complementary to at least one mutant allele is a gRNA.

75. The method of claim 71, wherein the at least one nucleotide sequence that is complementary to at least one mutant allele on a target gene is selected from an siRNA, an shRNA, an miRNA, an antisense RNA, or an antagomir RNA.

76. The method of claim 71, wherein the mutant allele is encoded by a target sequence on the target gene.

77. The method of claim 71, wherein the at least one nucleotide sequence that is complementary to at least one mutant allele on a target gene hybridizes to a target sequence on the target gene in a cell in the subject.

78. The method of claim 71, wherein the target gene is *TCF4* or *COL8A2*.

79. The method of claim 71, wherein at least one target sequence is selected from the group consisting of SEQ ID NOs: 1-1084.

80. The method of claim 71, wherein at least one target sequence is specific to the *TCF4* gene, and the target sequence is selected from SEQ ID NOs: 1-190.

81. The method of claim 71, the target sequence is specific to the *COL8A2* gene and the target sequence is selected from SEQ ID NOs: 191-1084

82. The method of claim 71, wherein the delivery system further comprises a repair template.

83. The method of claim 82, wherein the repair template is selected from the group consisting of a DNA repair template, an mRNA repair template, an siRNA repair template, an miRNA repair template, and an antisense oligonucleotide repair template.

84. The method of claim 74, wherein the gRNA hybridizes to a target sequence of the target gene in a cell in the subject.
85. The method of claim 71, wherein the delivery system further comprises a promoter.
86. The method of claim 85, wherein the promoter is optimized for use with an AAV5, AAV6, or AAV8 vector.
87. The method of claim 85, wherein the promoter is tissue specific, and when operably linked with the AAV vector or the nucleotide that is a sequence that is complementary to at least one mutant allele on a target gene is active in the eye.
88. The method of claim 87, wherein the tissue specific promoter is active in the cornea.
89. The method of claim 87, wherein the tissue specific promoter is active in the endothelium of the cornea.
90. The method of claim 71, wherein the delivery system is administered to the subject via injection into the eye.
91. The method of claim 71, wherein the delivery system is administered to the subject via injection to the anterior portion of the eye.
92. The method of claim 71, wherein the delivery system is administered to the corneal stroma, corneal limbus, onto the epithelial surface of the cornea, or onto the endothelial membrane of the cornea
93. The method of claim 71, wherein the delivery system is administered to the subject via intracameral injection.
94. The method of claim 71, which is suitable for treating a disease or condition in the eye.

95. The method of claim 94, wherein the disease or condition in the eye is a disease or condition of the cornea.
96. The method of claim 95, wherein the disease or condition of the cornea is a superficial corneal dystrophy, anterior corneal dystrophy, corneal stromal dystrophy, or posterior corneal dystrophy.
97. The method of claim 96, wherein the disease or condition of the cornea is a posterior corneal dystrophy.
98. The method of claim 97, wherein the posterior corneal dystrophy is selected from the group consisting of : Fuchs endothelial corneal dystrophy (FECD; both early and late onset), posterior polymorphous dystrophy (PPCD; types 1, 2, and 3), congenital endothelial dystrophy (types 1 and 2), and X-linked endothelial corneal dystrophy.
99. The method of claim 98, wherein the corneal dystrophy is FECD.
100. A method of treating a disease or condition of the cornea caused by a mutant allele of a gene that comprises trinucleotide repeats (TNRs) and/or a point mutation in a subject in need thereof, said method comprising:
- a) excising at least a portion of the trinucleotide repeats (TNRs) within the gene, comprising:
 - i) providing an AAV5, AAV6, or AAV8 vector which comprises one or more nucleotide sequences coding for one or more CRISPR guide RNAs targeting a sequence within the TNRs, 5' of the TNRs, 3' of the TNRs, or combination thereof; and
 - ii) administering the vector to the cornea; and/or
 - b) correcting the point mutation of the gene or gene product comprising:
 - i) providing an AAV5, AAV6, or AAV8 vector comprising one or more nucleotide sequences coding one or more CRISPR guide RNAs targeting a sequence in the gene associated with a point mutation in the gene product; and
 - ii) administering the vector to the cornea;
- wherein said one or more nucleotide sequences are preferentially expressed in the cornea.

101. The method of claim 100, wherein the target gene is *TCF4* or *COL8A2*.
102. The method of claim 100, wherein at least one target sequence is selected from the group consisting of SEQ ID NOs: 1-1084.
103. The method of claim 100, wherein at least one target sequence is specific to the *TCF4* gene, and the target sequence is selected from SEQ ID NOs: 1-190.
104. The method of claim 100, wherein the target sequence is specific to the *COL8A2* gene and the target sequence is selected from SEQ ID NOs: 191-1084.
105. The method of claim 100, wherein two guide RNAs are used.
106. The method of claim 100, wherein at least one guide RNA comprises a crRNA sequence that is complementary to at least one target sequence selected from SEQ ID NOs: 1-1084.
107. The method of claim 100, wherein at least one guide RNA comprises a guide sequence selected from the group consisting of SEQ ID NOs: 1089-1278.
108. The method of claim 100, wherein the TNRs are located in intron 3 of the *TCF4* gene.
109. The method of claim 100, wherein at least one guide RNA comprises a guide sequence that is complementary to at least one target sequence of the *TCF4* gene, and wherein the target sequence is selected from SEQ ID NOs: 1-190.
110. The method of claim 109, wherein two guide RNA are used, and wherein one guide RNA is complementary to a target sequence 5' of the TNRs, and the other guide is complementary to a target sequence 3' of the TNRs.
111. The method of claim 100, wherein the point mutations are located in the *COL8A2* gene, and wherein the target sequences are selected from SEQ ID NOs: 1064-1084.

112. The method of claim 100, wherein the AAV vector comprises a Cas protein.
113. The method of claim 112, wherein the Cas protein is Cas9 nuclease.
114. The method claim 100, wherein the TNRs are located in intron 3 of the *TCF4* gene.
115. The method of claim 113, wherein the Cas9 nuclease cleaves the TNRs.
116. The method of claim 100, wherein two gRNA are used, each comprising a guide sequence, and wherein one guide sequence directs a nuclease to a first location on intron 3 of the *TCF4* gene, and another guide sequence directs a nuclease to a second location on intron 3 of the *TCF4* gene.
117. The method of claim 113, wherein the nuclease cleaves the intron 3 of *TCF4*, and excises a fragment of nucleic acid between the first and second cleavage locations.
118. The method of claim 117, wherein the excised fragment of nucleic acid contains one or more TNRs.
119. The method of claim 100, suitable for treating a disease or condition associated with TNRs.
120. The method of claim 100, suitable for treating a disease or condition associated with TNRs in intron 3 of the *TCF4* gene.
121. The method of claim 100, which is suitable for treating a disease or condition associated with point mutations on the *COL8A2* gene.
122. The method of claim 100, wherein the vector further comprises a repair template.

123. The method of claim 122, wherein the repair template is selected from the group consisting of a DNA repair template, an mRNA repair template, an siRNA repair template, an miRNA repair template, and an antisense oligonucleotide repair template.
124. The method of claim 100, wherein the vector further comprises a promoter.
125. The method of claim 124, wherein the promoter is optimized for use with an AAV5, AAV6, or AAV8 vector.
126. The method of claim 124, wherein the promoter is tissue specific, and when operably linked with the AAV vector or the nucleotide that is a sequence that is complementary to at least one mutant allele on a target gene is active in the eye.
127. The method of claim 126, wherein the tissue specific promoter is active in the cornea.
128. The method of claim 127, wherein the tissue specific promoter is active in the endothelium of the cornea.
129. The method of claim 100, wherein the vector is administered to the subject via injection into the eye.
130. The method of claim 100, wherein the vector is administered to the subject via injection to the anterior portion of the eye.
131. The method of claim 100, wherein the vector system is administered to the corneal stroma, corneal limbus, onto the epithelial surface of the cornea, or onto the endothelial membrane of the cornea.
132. The method of claim 100, wherein the vector system is administered to the subject via intracameral (IC) injection.

133. The method of claim 100, wherein the one or more nucleotide sequences are preferentially expressed in the corneal endothelial cells as compared with other cells in the eye after IC injection.

134. The method of claim 100, which is suitable for treating a disease or condition in the eye.

135. The method of claim 134, wherein the disease or condition in the eye is a disease or condition of the cornea.

136. The method of claim 135, wherein the disease or condition of the cornea is a superficial corneal dystrophy, anterior corneal dystrophy, corneal stromal dystrophy, or posterior cornea dystrophy.

137. The method of claim 136, wherein the disease or condition of the cornea is a posterior corneal dystrophy.

138. The method of claim 137, wherein the posterior corneal dystrophy is selected from the group consisting of: Fuchs endothelial corneal dystrophy (FECD; both early and late onset), posterior polymorphous dystrophy (PPCD; types 1, 2, and 3), congenital endothelial dystrophy (types 1 and 2), and X-linked endothelial corneal dystrophy.

139. The method of claim 138, wherein the corneal dystrophy is FECD.

140. A method for down-regulating expression of a gene that is expressed in the cornea in a subject in need thereof, the method comprising administering to the subject a delivery system comprising:

- a) a nucleotide sequence, or portion thereof, of an AAV vector;
- b) a nucleic acid capable of down-regulating gene expression of at least one mutant allele on a target gene associated with diseases or conditions in the cornea; and
- c) administering the delivery system to the cornea.

141. The method of claim 140, wherein the nucleic acid capable of down-regulating gene expression is a CRISPR system nucleic acid sequence.

142. The method of claim 140, wherein the nucleic acid capable of down-regulating gene expression is a CRISPR-Cas system.

143. The method of claim 140, wherein the CRISPR-Cas system is a CRISPR-Cas9 system.

144. The method of claim 140, wherein the nucleic acid capable of down-regulating gene expression is selected from the group consisting of an antisense RNA, antagomir RNA, siRNA, shRNA.

145. The method of claim 140 further comprising at least one nucleotide sequence that is complementary to at least one mutant allele on a target gene associated with diseases or conditions in the cornea.

146. The method of claim 140, wherein the target gene is *TCF4* or *COL8A2*.

147. The method of claim 146, wherein at least one target sequence is selected from the group consisting of SEQ ID NOs: 1-1084.

148. The method of claim 146, wherein at least one target sequence is specific to the *TCF4* gene, and the target sequence is selected from SEQ ID NOs: 1-190.

149. The method of claim 146, wherein the target sequence is specific to the *COL8A2* gene and the target sequence is selected from SEQ ID NOs: 191-1084.

150. The method of claim 140, wherein the AAV vector serotype is selected from the group consisting of AAV5, AAV6, and AAV8.

151. The method of claim 140, wherein the AAV vector serotype is AAV5.

152. The method of claim 140, wherein the AAV vector serotype is AAV6.
153. The method of claim 140, wherein the AAV vector serotype is AAV8.
154. The method of claim 140, wherein the delivery system further comprises a repair template.
155. The method of claim 154, wherein the repair template is selected from the group consisting of a DNA repair template, an mRNA repair template, an siRNA repair template, an miRNA repair template, and an antisense oligonucleotide repair template.
156. The method of claim 140, wherein the delivery system further comprises a promoter.
157. The method of claim 156, wherein the promoter is optimized for use with an AAV5, AAV6, or AAV8 vector.
158. The method of claim 156, wherein the promoter is tissue specific, and when operably linked with the AAV vector or the nucleotide that is a sequence that is complementary to at least one mutant allele on a target gene is active in the eye.
159. The method of claim 158, wherein the tissue specific promoter is active in the cornea.
160. The method of claim 159, wherein the tissue specific promoter is active in the endothelium of the cornea.
161. The method of claim 140, wherein the target gene is preferentially expressed in the anterior portion of the eye.
162. The method of claim 140, wherein the delivery system and/or the nucleotide sequence capable of down-regulating at least one mutant allele on at least one target gene are preferentially expressed in the anterior portion after IC injection.

163. The method of claim 140, which is suitable for treating a disease or condition in the eye.
164. The method of claim 163, wherein the disease or condition in the eye is a disease or condition of the cornea.
165. The method of claim 164, wherein the disease or condition of the cornea is a superficial corneal dystrophy, anterior corneal dystrophy, corneal stromal dystrophy, or posterior cornea dystrophy.
166. The method of claim 165, wherein the disease or condition of the cornea is a posterior corneal dystrophy.
167. The method of claim 166, wherein the posterior corneal dystrophy is selected from the group consisting of: Fuchs endothelial corneal dystrophy (FECD; both early and late onset), posterior polymorphous dystrophy (PPCD; types 1, 2, and 3), congenital endothelial dystrophy (types 1 and 2), and X-linked endothelial corneal dystrophy.
168. The method of claim 167, wherein the corneal dystrophy is FECD.

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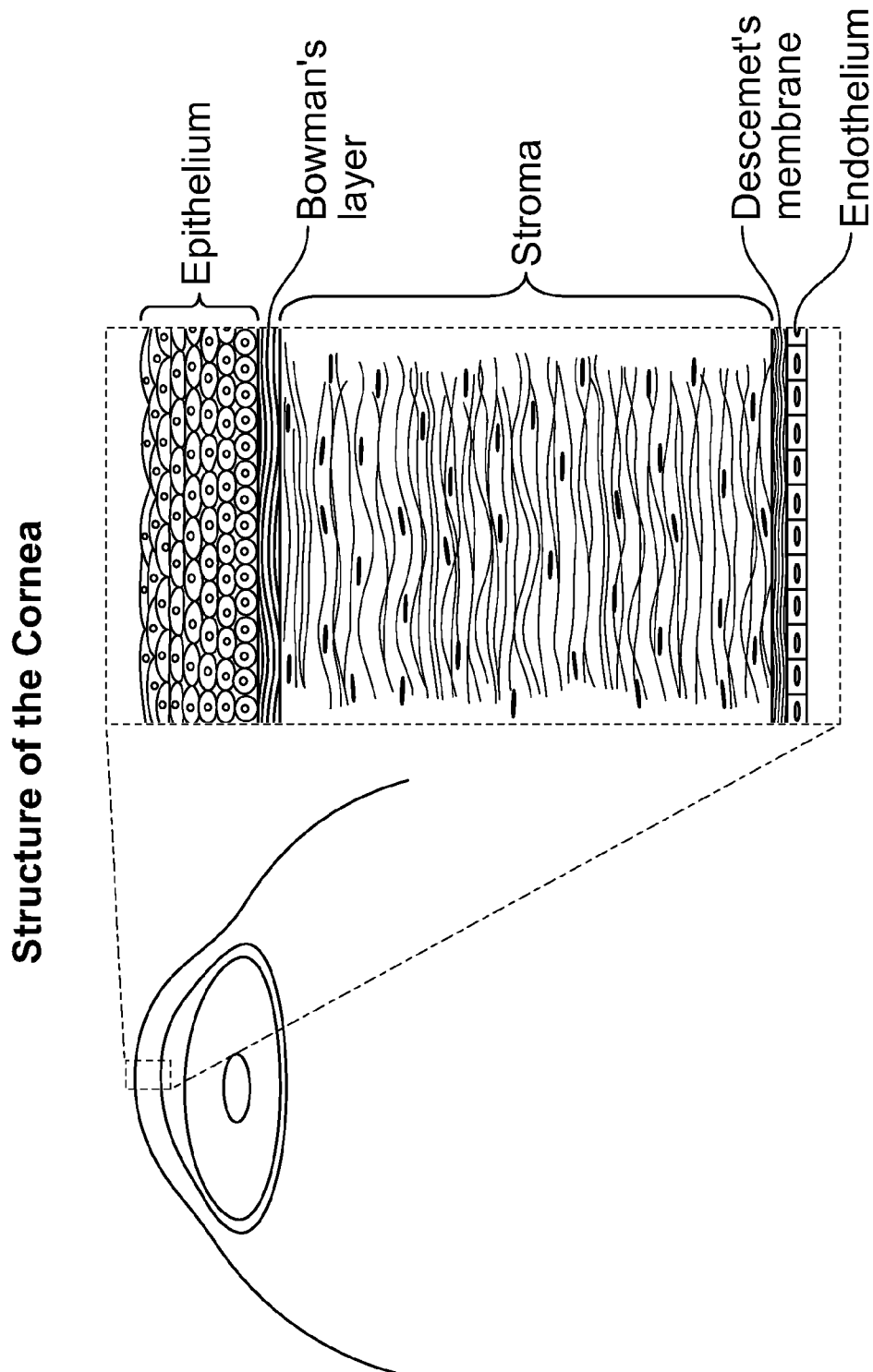


FIG. 1

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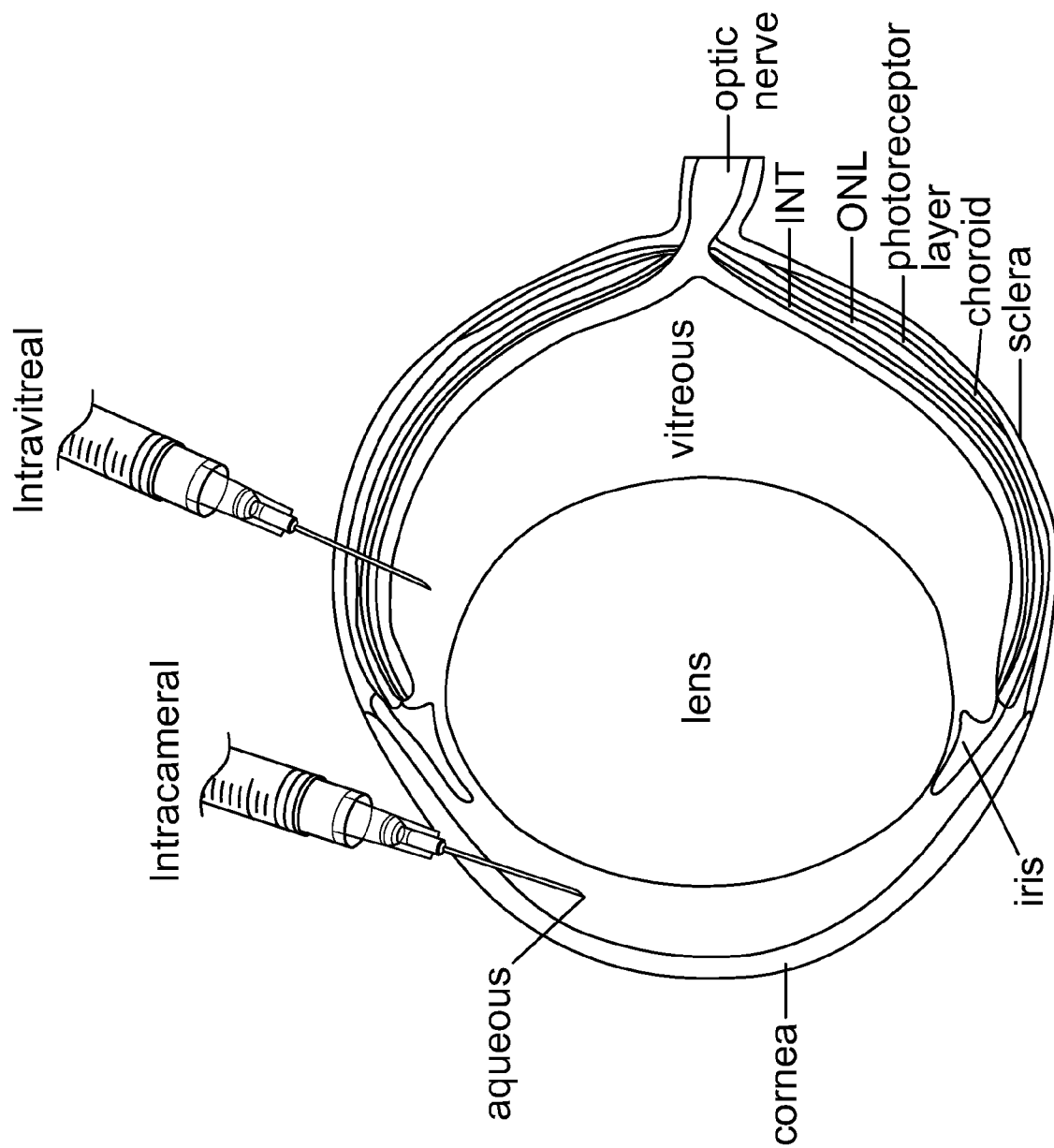


FIG. 2

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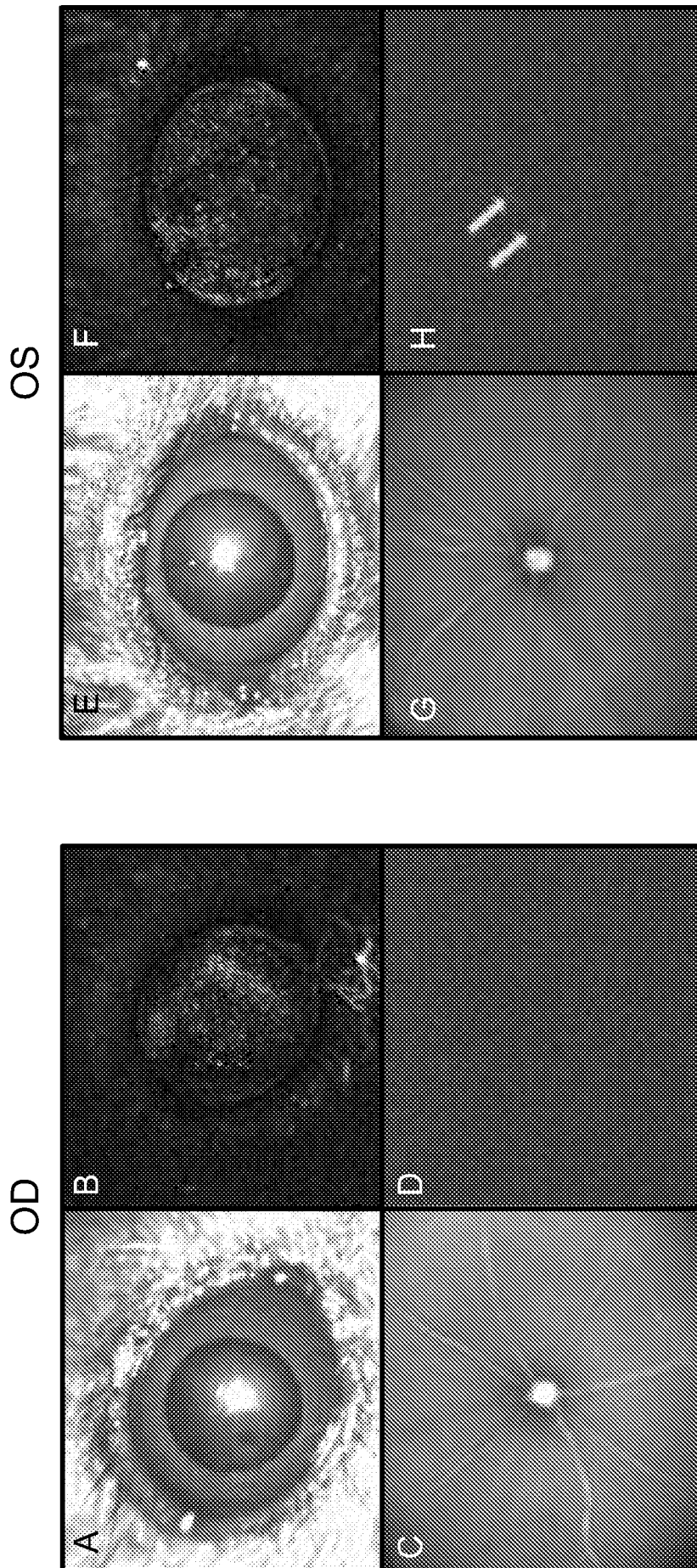


FIG. 3

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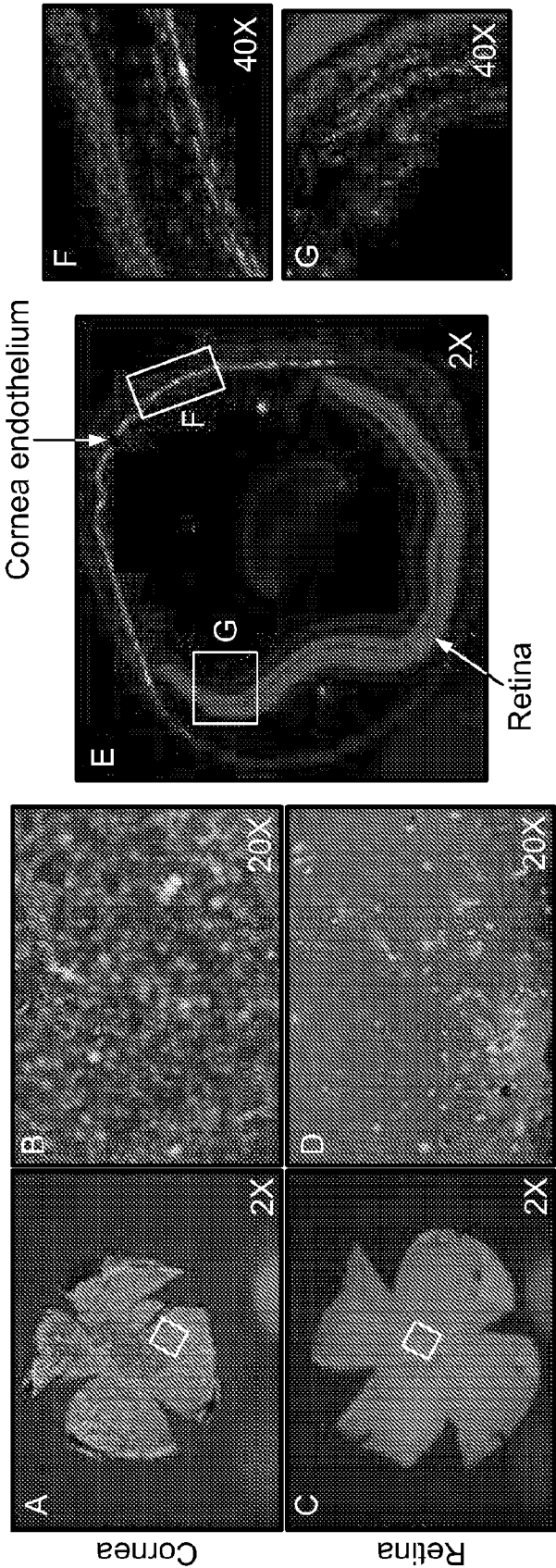


FIG. 4

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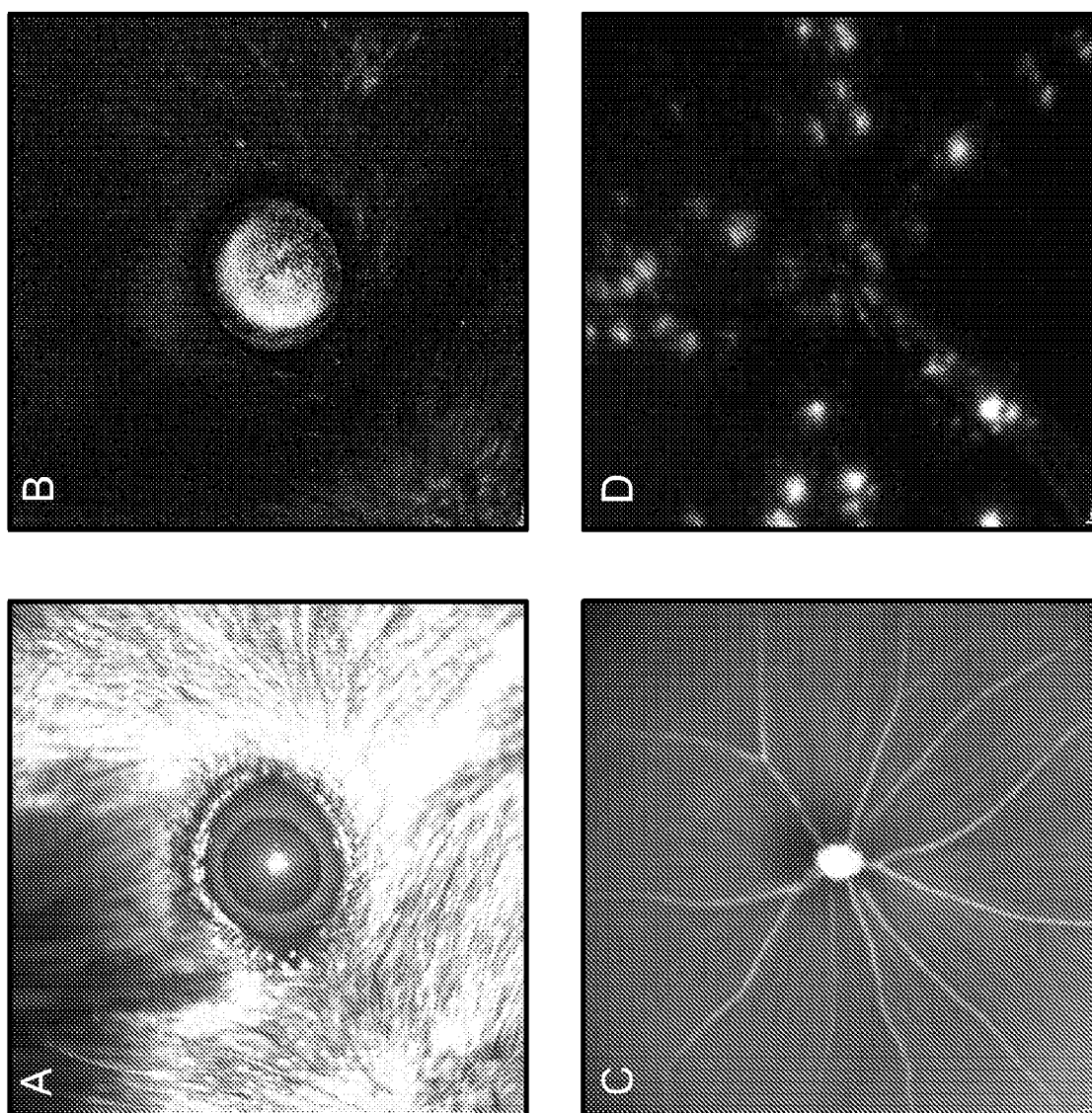


FIG. 5

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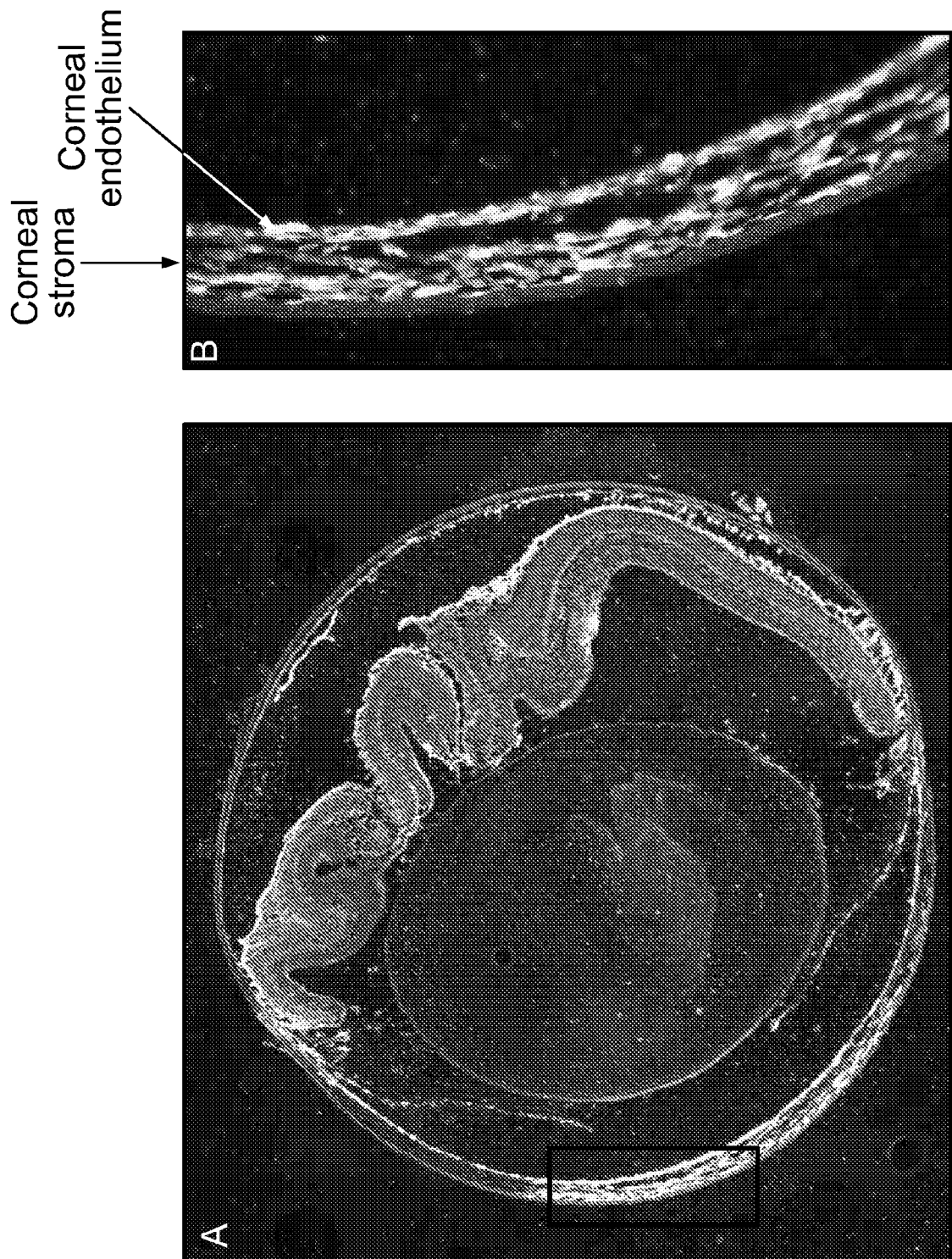
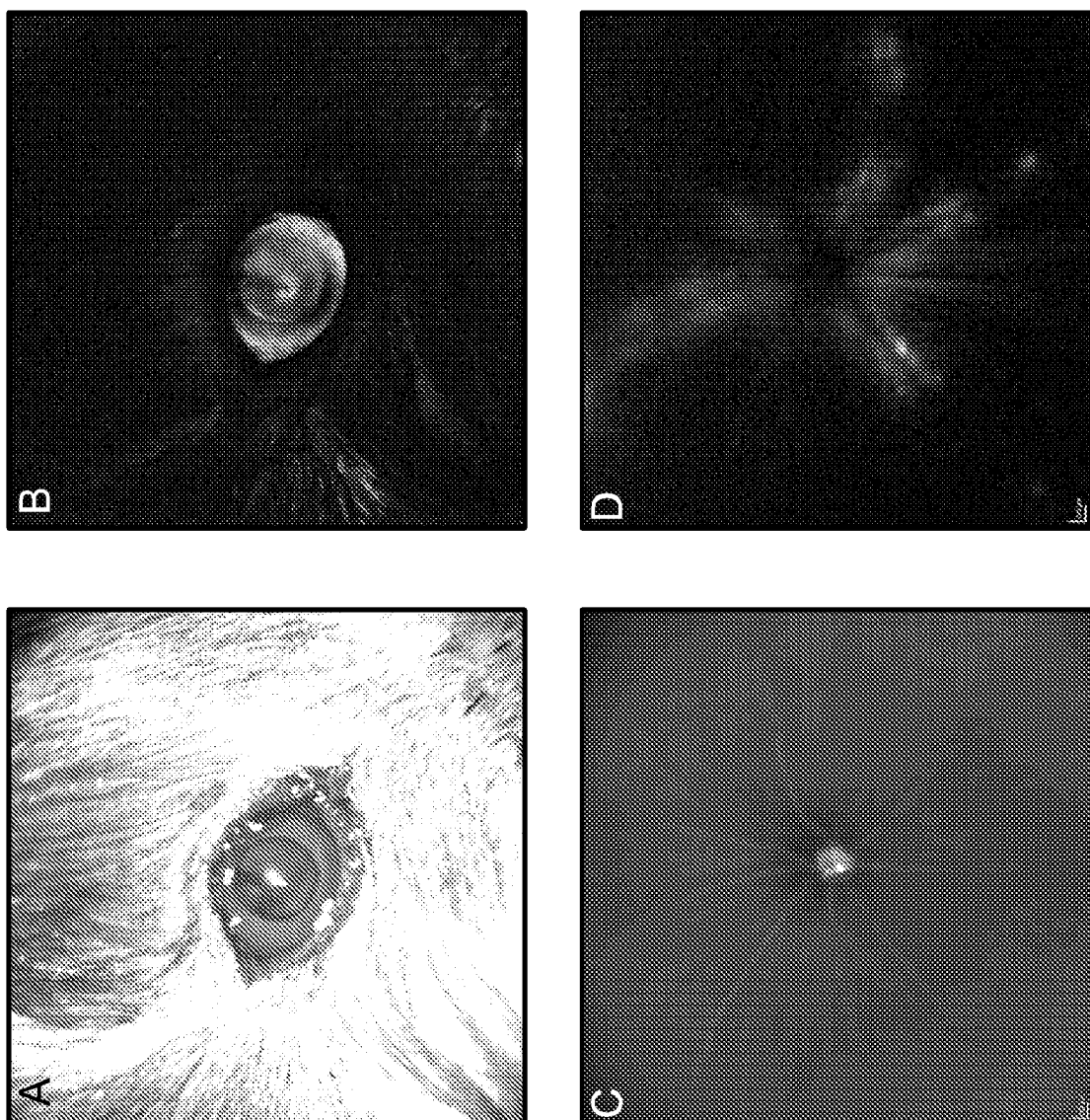


FIG. 6

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FIG. 7



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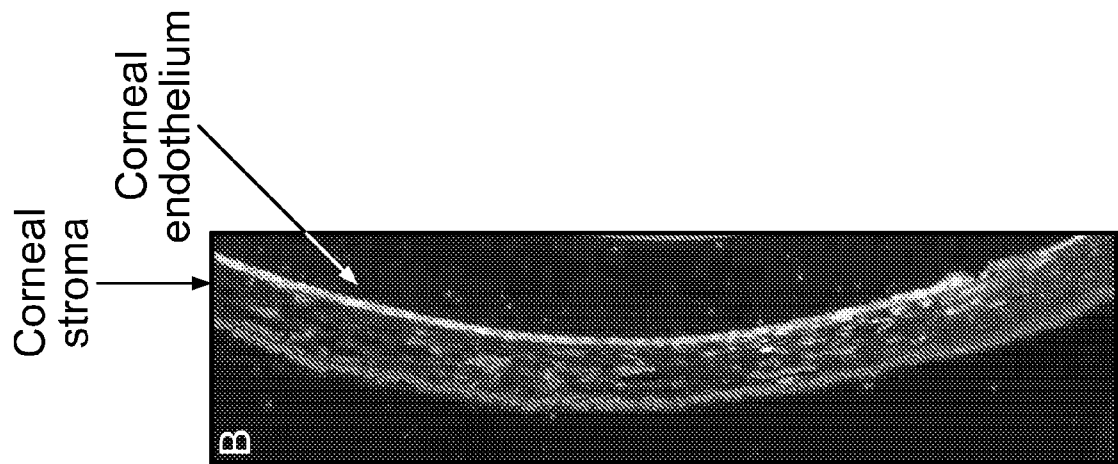
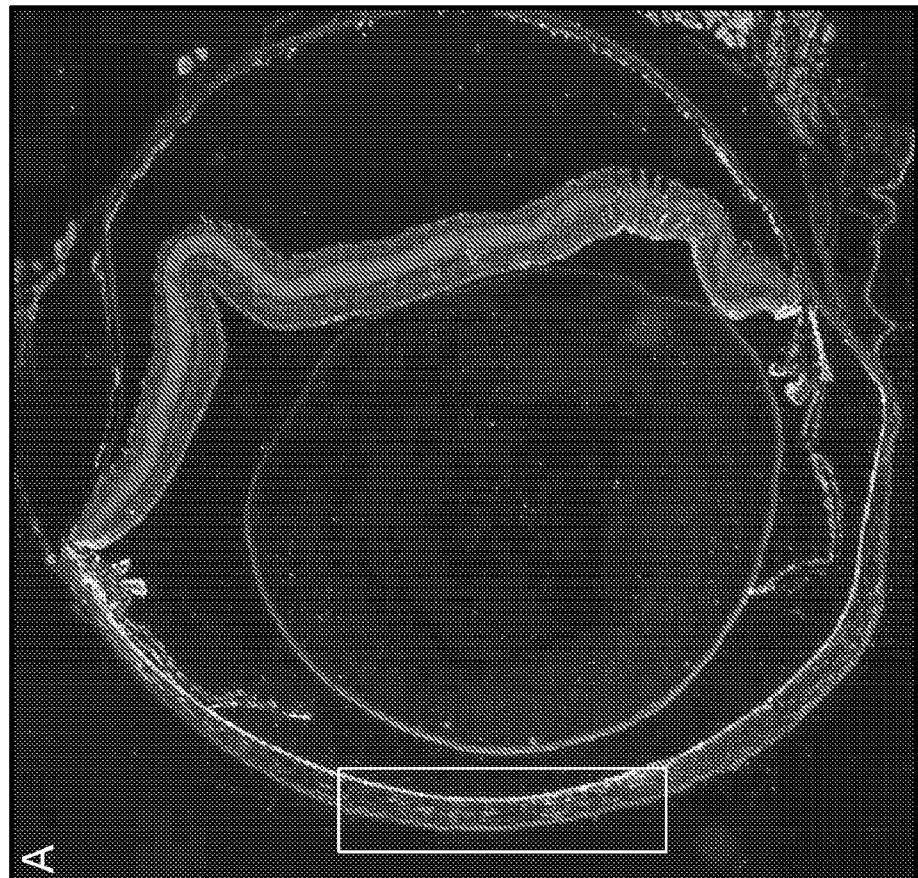


FIG. 8



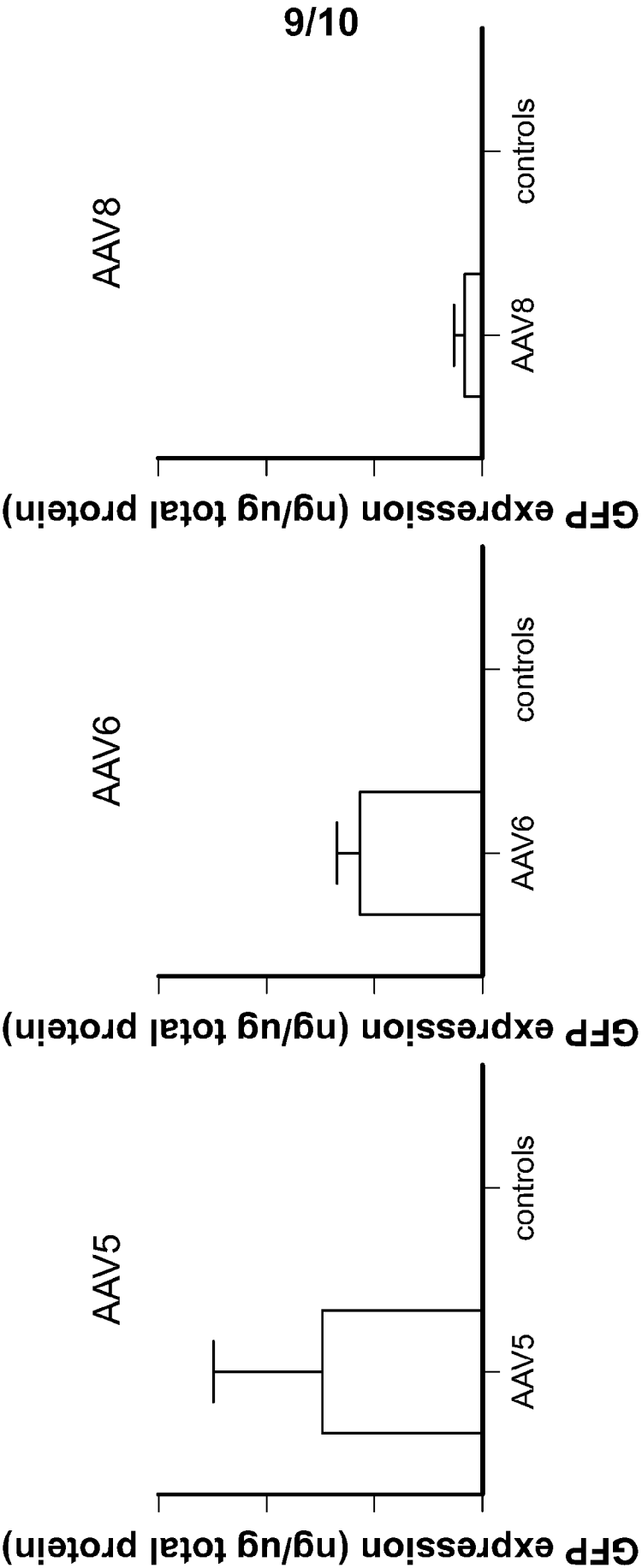


FIG. 9

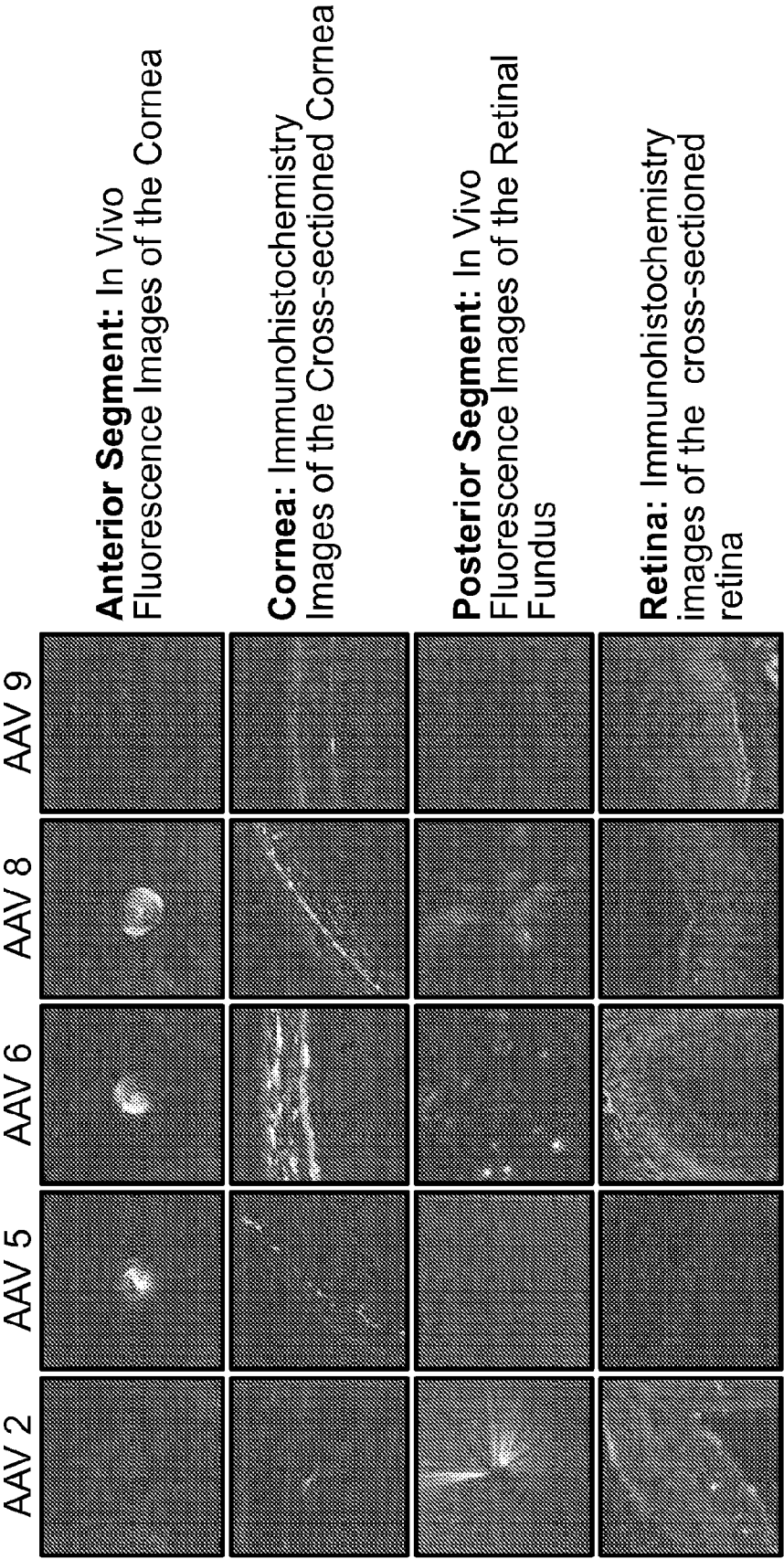


FIG. 10

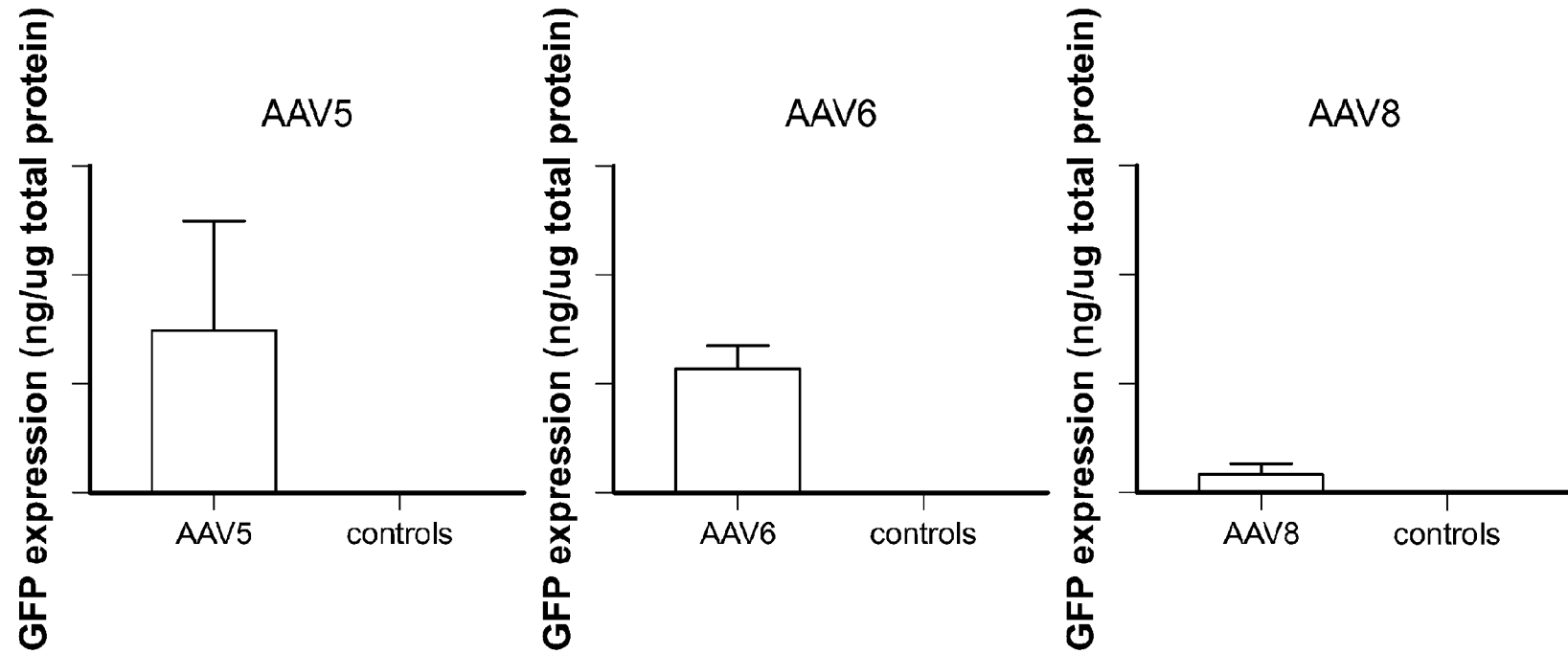


FIG. 9